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Case Report

Two Infant Cases of Chronic Hepatitis B Cirrhosis Treated with Lamivudine and Literatures Review

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1. Abstract

1.1. Objective: This study aimed to investigate the efficacy and safety of lamivudine treatment for infant children with Chronic Hepatitis B (CHB) cirrhosis.

1.2. Methods: Clinical features, laboratory examinations, efficacy and safety of lamivudine antiviral therapy for two infant cases with chronic hepatitis B cirrhosis who were treated and relative long-term followed up in our hospital were reported. Literatures on the treatment of chronic hepatitis B until December of 2017 were searched and summarized.

1.3. Results: The two HBeAg-positive infant patients with CHB presented with elevated ALT≥2ULN over six months. Liver biopsy scored CHB-G3-4S4e and CHB-G3S4e before antiviral treatment, respectively. Antiviral therapy of lamivudine (3mg/kg•d, qd, po) was administered to the two children patients when they were 1year and 1month old. The treatment duration lasted 2 years and 1 month. For Case 1, there was still volatile in ALT in the early stage of antiviral treatment. At 16 weeks of treatment, ALT trended to be normal. During 16 weeks to before 76 weeks, ALT fluctuated at 41-56 IU/L and AST 39-55 IU/L. From 76 weeks upon, the ALT became normal completely. At 24 weeks, HBeAg seroconversion occurred and HBV-DNA level began to be below the detection limit. For Case 2, ALT became normal at 24-week of treatment. HBeAg seroconversion occurred and HBV-DNA level became undetected at 12-week. Liver biopsy showed CHB-G1S3 and CHB-G0S0 before lamivudine was withdrawn in both two children, respectively. No obvious adverse reactions were observed during the antiviral treatment. The two children had been followed up for 4 years and 1.5 years after antiviral treatment withdraw, respectively. And the ALT keeps normal, HBeAg seroconversion is maintained and HBV-DNA level sustains below the detection limit.

1.4. Conclusion: There were obvious liver injuries and early liver cirrhosis in HBeAg-positive infant patients with CHB. Liver inflammation and cirrhosis can be reversed effectively by lamivudine antiviral therapy to a certain extent.

2. Keywords: Infant; Chronic hepatitis B; Antiviral treatment; Lamivudine (LAM)

3. Introduction

Hepatitis B is an infectious disease resulting liver damage caused by Hepatitis B Virus (HBV). About 2 billion people had infected HBV worldwide according to World Health Organization (WHO), including 240 million people with chronic HBV infection [1]. HBV infection in early life can develop into chronic infection easily, which becomes the main source of chronic hepatitis B (CHB) [2]. There is no standard antiviral therapy for children with CHB so far. We now report 2 infant cases of CHB cirrhosis aged 1-year-1-month treated with antiviral therapy of lamivudine (LAM). Liver inflammation was improved and cirrhosis was reversed after withdraw, and literatures were reviewed in this article.

4. Cases presentation

Clinical data and treatment process. Their parents were told all the regimens and signed informed consent before the antiviral therapy was administrated to children with CHB.

4.1. Case 1

Our Case 1 involved a male baby infected with HBV diagnosed at 9 months of his life with elevated biochemical transaminases. Then he visited and hospitalized our hospital. Physical examination: his consciousness was clear and good response, mild jaundice in sclera and skin, no petechiae bleeder or ecchymosis in skin. Breath sounds were coarse and symmetrical in double lungs. Heart sounds were strong and no splitting. Cardiac rhythm was regular. No pathological murmurs. Abdomen was distended and no dilated veins. Liver was pliable. Liver was touched 9cm under the right costal margin and 6cm in subxiphoid regions. Spleen was touched 4cm under the left costal margin. And spleen was soft. Borborygmus was normal. Muscle tensity of all limbs was normal and no swelling. The Nervous System (NS) was normal. Complete blood cells count, clotting function, biochemistry, serum HBV biomarkers, and HBV-DNA load were tested (Table 1 and 2). And HBV genotyped B. Co-infection of HAV, HCV, HEV, syphilis, HIV and TORCH were exclusive. Liver biopsy was performed and the pathology (Department of Pathology, Shanghai Medical School, and Fudan University) showed CHB-G3-4S4e (Figure 1). Treatment of liver protection and eczema was administrated, and liver function was improved. The infant patient was in a stable condition and released after14 days in hospital, taking medicine.

The child was followed-up in outpatient for 3 months after releasing. Biochemical transaminases were elevated (Table 1) ("before antiviral treatment"). Biochemical transaminases were retested before antiviral treatment, and it result ALT 123 IU/L, AST 196 IU/L. It had been over six months from the first time diagnosed as hepatitis B, and ALT≥2ULN, HBeAg-positive, HBV-DNA≥105IU/ml, which had antiviral indications for him and the child aged 1-year-1-month old at this time. Antiviral therapy of LAM (3 mg/kg•d, qd, po) was administrated to him considering the relatively interferon alpha (IFN-α) treatment contraindication of early liver cirrhosis and TB>34 μmol/L. Complete blood cells count, clotting function, biochemistry, serum HBV biomarkers, and HBV-DNA load and so on were monitored during the antiviral treatment follow-up outpatient. There was still volatile in ALT in the early stage of antiviral treatment. At 16 weeks of treatment, ALT trended to be normal. During 16 weeks to before 76 weeks, ALT fluctuated at 41-56 IU/L and AST 39-55IU/L. From 76 weeks upon, the ALT became normal completely. At 24 weeks, HBeAg seroconversion occurred and HBV-DNA level began to be below the detection limit (Table 1 and 2) "treatment process".

Complete blood cells count, clotting function, biochemistry, serum HBV biomarkers, and HBV-DNA load and so on were re-tested by 2-year treatment in outpatient (Table 1 and 2) "96-week treatment". It met the clinical end point of antiviral treatment according to Chinese Guide for Prevention and Treatment of Chronic Hepatitis B (2015) [3]. Liver biopsy was performed again, and it showed CHB-G1S3 (Figure 2). And then LAM was withdrawal 1 month later. The antiviral duration last 2 years and 1 month, and then the patient were followed-up in outpatient department after that regularly.

Table 1: Biochemistry and HBV biomarkers of Case 1

	First visit	Before treatment	Treatment process							After withdrawal				
			8w	16w	24w	36w	48w	72w	96w	0.5 y	1 y	2 ys	3 ys	4 ys
Age (yo)	$\frac{9}{12}$	$\frac{10}{12}-1\frac{2}{12}$	$1\frac{4}{12}$	$1\frac{5}{12}$	$1\frac{7}{12}$	$1\frac{10}{12}$	$2\frac{7}{12}$	$3\frac{1}{12}$	$3\frac{7}{12}$	$4\frac{1}{12}$	$4\frac{7}{12}$	$5\frac{7}{12}$	$6\frac{7}{12}$	$7\frac{7}{12}$
TB(5.1-17.1mmol/L)	81.1	31.1-121.3	18.4	9.6	10.7	7.1	6.4	6.1	4.6	3.9	4.4	5.4	6.2	8
DB(0-6mmol/L)	69.8	25-104.5	13.4	6.6	6.4	3.3	4.2	2.3	1.7	1.1	1.2	1.8	2.1	2.5
ALT(0-40U/L)	396	88-461	131	45	47	43	44	27	19	20	13	15	37	37
AST(0-40U/L)	499	71-499	99	48	55	56	39	29	21	26	22	18	39	27
AKP(42-383U/L)	469	388-576	434	605	669	471	516	352	294	299	332	353	343	290
GGT(7-50U/L)	110	50-881	96	35	36	38	32	26	26	37	28	33	30	56
CHEW(185-461U/L)	129	96-146	198	203	215	216	211	291	282	297	326	415	406	358
TBA(0-10mmol/L)	238.1	143.6-361.6	288.2	178.7	206.6	83.9	172.4	18.3	17.4	12.5	8.5	6.5	13	3.8
A(35-55g/L)	41.7	39.7-43.3	42.9	42.8	44.8	43.9	44.6	47	43.6	43.5	46.4	45.2	46.5	45.2
G(20-30g/L)	36.9	33.6-39.6	36.1	28	/	29.8	28.8	24.4	22.9	27	24	24.3	27.5	23.3
BUN（2.5-6.5mmol/L）	3.7	/				/	/	/	4.7	/	/	/	8.4	6.1
Cr（20-110mmol/L）	16								12				27	24
HBsAg(0-0.5ng/ml)	225	225	/	/	225	/	225	225	225	202.26	225	222	225	222
HBsAb(0-10mIU/ml)	-	-			-		-	-	-	-	-	-	-	-
HBeAg(0-0.5PEIU/ml)	3.13	3.13			-		-	-	-	-	-	-	-	-
HBeAb(0-0.2PEIU/ml)	-	-			1.76		3.975	2.05	2.05	2.05	2.05	3.98	1.88	1.88
HBcAb(0-0.9PEIU/ml)	3.46	3.07			2.025		2.025	3	2.39	3.87	3.87	3.6	3.6	11.11
HBV-DNA(<1000IU/ml)	>1.00×108	9.45×106			<103		<103	<103	<103	<103	<103	<103	<103	<103

Table 2: CBC, clotting and AFP of Case 1

	First visit	Before treatment	Treatment process							After withdrawal				
			8w	16w	24w	36w	48w	72w	96w	0.5 y	1 y	2 ys	3 ys	4 ys
Age (yo)	$\frac{9}{12}$	$1\frac{2}{12}$	$1\frac{4}{12}$	$1\frac{5}{12}$	$1\frac{7}{12}$	$1\frac{10}{12}$	$2\frac{7}{12}$	$3\frac{1}{12}$	$3\frac{7}{12}$	$4\frac{1}{12}$	$4\frac{7}{12}$	$5\frac{7}{12}$	$6\frac{7}{12}$	$7\frac{7}{12}$
WBC（4-10×10^9/L）	11.2	12.1	/	12.4	11.7	9	9.7	7.2	7	/				
NEUT%（45-77%）	28.4	34.1		47	33.2	34.6	28.4	40	37.1					

Hb(110-160g/L)	100	117		126	125	116	133	112	130					
BPC（100-300×10⁹/L）	3.55	285		228	250	297	311	257	307					
ATPP（28-44.5s）	36.5	35.7	/	/	/	/	/	/	34.6	/				
INR(0.8-1.2)	0.98	1.02							1					
PT(12-14.8s)	12.7	13.1							13.1					
PTA(80%-120%)	103	97							100					
TT(14-21s)	18.9	20.2							17.4					
AFP	/	/	/	/	/	/	21.85	10.98	5.54	3.11	2.18	1.8	1.6	2.8
"-": negative result. "/": no test or no result.														

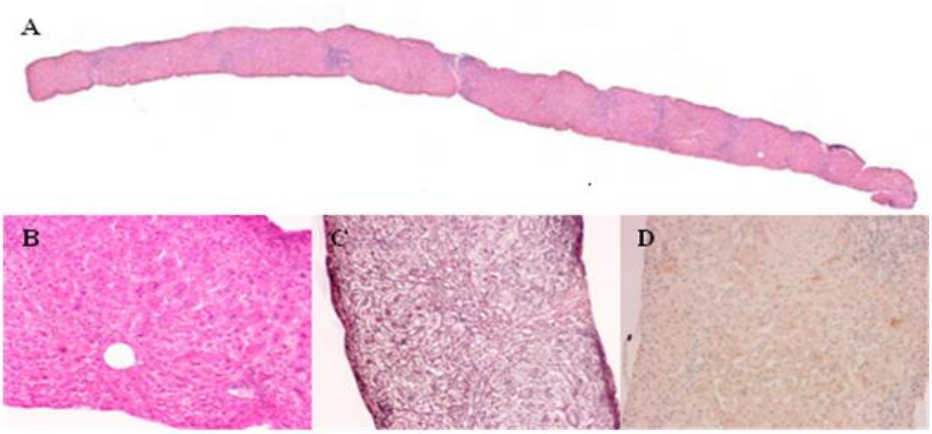

Figure 1: Liver pathology before antiviral treatment of Case 1.
Picture A shows microscopic panorama of liver pathology before antiviral treatment, HE staining. The structures of hepatic lobules were messy. Liver false lobules were formed locally. Point necrosis was scattered in lobules. Apoptotic bodies were formed in hepatic cords. Hepatocellular cholestasis was formed, and capillary bile duct was expanded with bile acid formation. Picture B shows the HE staining of portal area. Moderate inflammation was formed in portal areas, liver boundary board was damaged with interface hepatitis and bridge necrosis formation. Picture C shows Reticular and Masson staining. Early liver cirrhosis was formed. Picture D shows the HBsAg dyeing, which was strongly positive.

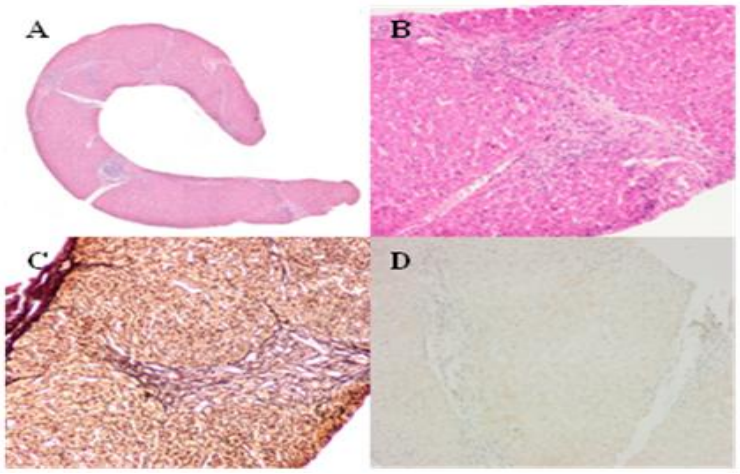

Figure 2: Liver pathology before LAM withdrawal of Case 1.
Picture A shows microscopic panorama of liver pathology before LAM withdrawal, HE staining. The structures of hepatic lobules were regular. No degeneration necrosis was found in liver cells. Mild-to-moderate inflammation was formed in portal area. Picture B shows the HE staining of portal area. Mild-to-moderate inflammation was seen in portal area, but no damage was found in liver boundary board. Picture C shows Reticular and Masson staining. Fibrosis intervals were formed extensively in portal areas. No obvious false lobule was seen. Picture D shows the HBsAg dyeing, which was mildly positive.

4.2. Case 2

Case 2 was so similar to Case 1, which involved a male baby infected with HBV diagnosed at 6 months of his life with elevated biochemical transaminases. He visited and hospitalized our hospital. Physical examination: his consciousness was clear and good response, mild jaundice in sclera and skin, no petechiae bleeder or ecchymosis in skin. Breath sounds were coarse and symmetrical in double lungs. Heart sounds were strong and no splitting. Cardiac rhythm was regular. No pathological murmurs. Abdomen was distended and no dilated veins. Liver was pliable. Liver was touched 2cm under the right costal margin and 1cm in subxiphoid regions. Spleen was unreachable under the left costal margin. And spleen was soft. Borborygmus was normal. Muscle tensity of all limbs was normal and no swelling. NS(-). Complete blood cells count, clotting function, biochemistry, serum HBV biomarkers, and HBV-DNA load were tested (Table 3 and 4).

And HBV genotyped C. Co-infection of HAV, HCV, HEV, syphilis, HIV and TORCH were exclusive. Liver biopsy was performed and the pathology (Department of Pathology, Shanghai Medical School, and Fudan University) showed CHB-G3S4e (Figure 3). Biochemical transaminases were retested before antiviral treatment, and it result ALT 235 IU/L, AST 117 IU/L. It had been over six months from the first time diagnosed as hepatitis B, and ALT≥2ULN, HBeAg-positive, HBV-DNA≥105IU/ml, which had antiviral indications for him and the child aged 1-year-1-month old at that time. Treatment of liver protection and eczema, and antiviral therapy of LAM (3 mg/kg•d, qd, po) was administrated to him considering the relatively IFN-α treatment contraindication of early liver cirrhosis.

Complete blood cells count, clotting function, biochemistry, serum HBV biomarkers, and HBV-DNA load and so on were monitored during the antiviral treatment follow-up outpatient. There was still volatile in ALT in the early stage of antiviral treatment. At 24 weeks of treatment, ALT became and kept normal. At 12 weeks, HBeAg seroconversion occurred and HBV-DNA level became undetected (Table 3 and 4) "treatment process".

Complete blood cells count, clotting function, biochemistry, serum HBV biomarkers, and HBV-DNA load and so on were re-tested by 2-year treatment in outpatient (Table 3 and 4) "96-week treatment". It met the clinical end point of antiviral treatment according to Chinese Guide for Prevention and Treatment of Chronic Hepatitis B (2015) [3]. Liver biopsy was performed again, and it showed CHB-G0S0 (Figure 4). And then LAM was withdrawal 1 month later. The antiviral duration last also 2 years and 1 month, and then the patient was followed-up in outpatient after that regularly.

Follow-up after antiviral treatment withdraw Biochemistry, serum HBV biomarkers, HBV-DNA load, AFP and so on were monitored after LAM withdraw in both two children patients regularly (six months, 1 year, 2 years, 3 years...). And these two children are still in follow-up. Biochemical Transaminases keep normal, HBeAg seroconversion sustains, and HBV-DNA remains undetected (Table 1 and 3) “after drug withdrawal”.

Table 3: Biochemistry and HBV biomarkers of Case 2

	Before treatment	Treatment process					After withdrawal		
		12w	24w	48w	72w	96w	EOT-3m	EOT-6m	EOT-18m
Age (yo)	$1\frac{1}{12}$	$1\frac{4}{12}$	$1\frac{7}{12}$	$2\frac{1}{12}$	$2\frac{7}{12}$	$3\frac{1}{12}$	$3\frac{1}{12}$	$3\frac{9}{12}$	$4\frac{7}{12}$
TB(5.1-17.1mmol/L)	6.4	3.8	5.9	4.1	4.9	4.8	8.7	5.9	7.6
DB(0-6mmol/L)	2.6	1.3	2	1.7	2.1	1.4	2.8	1.4	2.4
ALT(0-40U/L)	235	106	20	17	26	13	12	15	14
AST(0-40U/L)	117	181	31	29	25	21	20	23	21
AKP(42-383U/L)	313	345	297	366	329	275	320	327	334
GGT(7-50U/L)	50	59	19	21	16	13	16	15	16
CHEW(185-461U/L)	258	308	311	264	379	374	409	473	605
TBA(0-10mmol/L)	8.3	30.7	6.4	4	12.2	16.7	3.9	12.8	8.4
A(35-55g/L)	42.1	43.6	42.6	44.2	45.4	44.9	46.3	43.9	45
G(20-30g/L)	23.1	22.2	20.9	22	19	20	18.7	24.1	19.8
BUN（2.5-6.5mmol/L）	3.7	/	/	/	/	3.6	/	/	/
Cr（20-110mmol/L）	16	/	16	25	/	26	/	/	/
HBsAg(0-0.5ng/ml)	225	225	225	225	225	225	225	225	225
HBsAb(0-10mIU/ml)	-	-	-	-	-	-	-	-	-
HBeAg(0-0.5PEIU/ml)	1.63	-	0.02	-	-	-	-	-	-
HBeAb(0-0.2PEIU/ml)	-	>2.05	>>2.05	>2.05	>2.05	>2.05	>2.05	>2.05	3.98
HBcAb(0-0.9PEIU/ml)	>3.87	>3.87	>>3.87	3.75	>3.87	>3.87	>3.87	3.24	3.6
HBV-DNA(<1000IU/ml)	7.32×106	9.51×102	<500	<500	<500	<500	<500	<1000	<1000

“-”: negative result. “/”: no test or no result.

Table 4: CBC, clotting and AFP of Case 2

	Before treatment	Treatment process					After withdrawal		
		12w	24w	48w	72w	96w	EOT-3m	EOT-6m	EOT-18m
Age (yo)	$1\frac{1}{12}$	$1\frac{4}{12}$	$1\frac{7}{12}$	$2\frac{1}{12}$	$2\frac{7}{12}$	$3\frac{1}{12}$	$3\frac{1}{12}$	$3\frac{9}{12}$	$4\frac{7}{12}$
WBC（4-10×10⁹/L）	5.6	/	7.6	12.5	7.9	6.8	/		
NEUT%（45-77%）	/		29.7	41	30.7	35.2			
Hb(110-160g/L)	132		134	138	139	134			
BPC（100-300×10⁹/L）	362		230	319	255	275			
ATPP（28-44.5s）	30.1	/	/	/	/	28.5	/		
INR(0.8-1.2)	1					0.93			
PT(12-14.8s)	13.2					12.4			
PTA(80%-120%)	100					114			
TT(14-21s)	16.1					16.3			
AFP	/	9.85	5.92	4.33	2.63	2.84	1.78	2.58	/

“-”: negative result. “/”: no test or no result.

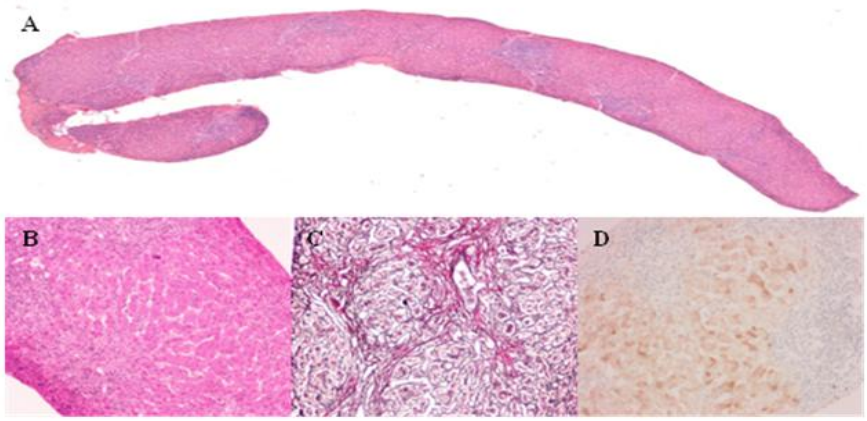

Figure 3: Liver pathology before antiviral treatment of Case 2.
Picture A shows microscopic panorama of liver pathology before antiviral treatment, HE staining. The structures of hepatic lobules were messy. Liver false lobules were formed locally. Point necrosis was scattered in lobules. Apoptotic bodies were formed in hepatic cords. Hepatocellular cholestasis was formed, and capillary bile duct was expanded with bile acid formation. Picture B shows the HE staining of portal area. Moderate inflammation was formed in portal areas, liver boundary board was damaged with interface hepatitis and bridge necrosis formation. Picture C shows Reticular and Masson staining. Early liver cirrhosis was formed. Picture D shows the HBsAg dyeing, which was strongly positive.

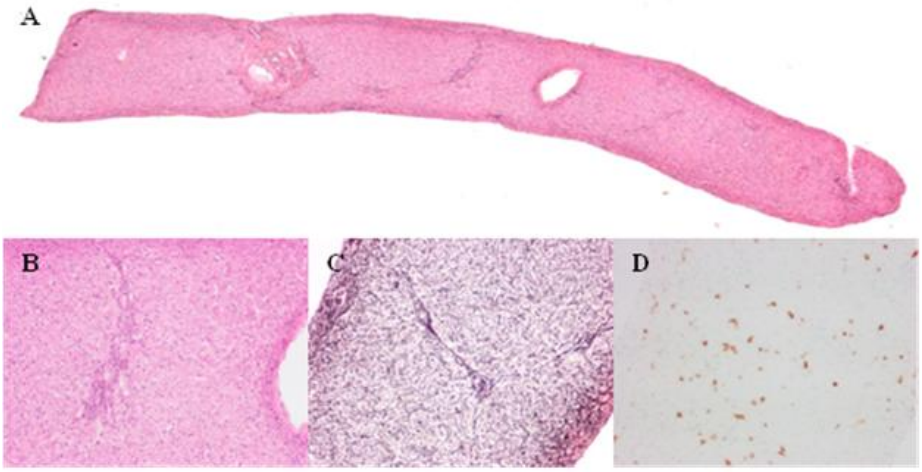

Figure 4: Liver pathology before LAM withdrawal of Case 2.
Picture A shows microscopic panorama of liver pathology before LAM withdrawal, HE staining. The structures of hepatic lobules were regular. No degeneration necrosis was found in liver cells. No inflammation was formed in portal area. Picture B shows the HE staining of portal area. No inflammation or damage was found in liver boundary board, and no fibrosis was formed. Picture C shows Reticular and Masson staining. No obvious fibrosis or false lobule was seen. Picture D shows the HBsAg dyeing, which was positive but not so strong.

5. Discussion

Natural history of HBV infection depends on the interaction between virus and host. The age of HBV infection is the main factor of chronic infection. Among patients infected HBV in perinatal period and early childhood, 90% and 25% ~ 30% will develop chronic infection, respectively. And only 5% ~ 10% will develop chronic infection if they are infected after 5 years old [4, 5]. Most HBV infections occur in perinatal infection or infant period in China. Generally speaking, the natural history of HBV infection can be divided into four phases artificially: immune tolerance phase, immune clearance phase, inactive or low-copy (non-copy) phase and reactive phase [6]. But not all patients infected with HBV experience the four phases. Most patients infected HBV in youth and adulthood enter immune clearance phase directly but without immune tolerance phase. In immune tolerance phase, serum HBsAg and HBeAg are positive, HBV-DNA level is high (> 200000 IU/mL), ALT is normal, liver histology shows no obvious abnormality or mild inflammatory necrosis, no or only slow progress of liver fibrosis. Immune clearance phase is characterized by HBV-DNA loads > 2000 IU/mL, continuous or intermittent ALT elevation, moderate or severe inflammatory necrosis of liver histology, rapid progress of fibrosis and even some can develop liver cirrhosis and liver failure. In this paper, these two HBeAg-positive cases were HBsAg-positive, repeatedly elevated transaminases, HBV-DNA≥105 IU/ml, which had already entered the immune clearance phase. And liver histology was characterized by severe inflammation, necrosis and early liver cirrhosis, which had antiviral indications.

The aim of treatment for Chronic Hepatitis B (CHB) is to maximize the long-term suppress HBV replication, relieve inflammatory cell necrosis in the liver and liver fibrosis, delay and reduce the liver failure, decompensate cirrhosis, HCC and other complications, then

to improve the quality of life and prolong survival time [3, 7]. It depends mainly on clinical manifestations, laboratory examination (serum ALT, HBV biomarkers, HBV-DNA load) and the severity of liver pathology to determine whether to start antiviral treatment [7-10]. There are mainly two categories of antiviral drugs for CHB adults currently, IFN-α and nucleoside analogues (acid) (NAs) [7]. Due to the particularity of children's growth and development, drugs can be used for HBV antiviral treatment in children are only IFN-α, including polyethylene glycol interferon alpha (Peg-IFN-α) and some nucleoside (acid) analogues (NAs) at present, and the choice is limited [11]. Chinese Guide for Prevention and Treatment of Chronic Hepatitis B (2015) recommends that children infected HBV are often in immune tolerance phase, which antiviral treatment is usually not considered. However, antiviral therapy should be administrated for those who enter immune clearance phase timely. But problems of safety and resistance should be taken into consideration for a long-term antiviral treatment [3]. The two HBeAg-positive CHB cases had entered the immune clearance phase and aged older than 1 years old, which had good indications of antiviral treatment. Antiviral therapy of LAM was administrated to the two children after their parents signed the informed consents, considering the relatively IFN-α treatment contraindication of early liver cirrhosis and TB>34 μmol/L. The treatment duration lasted 2 years and 1 month. The two children had been followed up for 4 years and 1.5 years after antiviral treatment withdraw, respectively. And the ALT keeps normal, HBeAg seroconversion is maintained and HBV-DNA level sustains below the detection limit, which achieve satisfactory clinical cure [3, 7]. And two children are still in follow-up.

NAs are safe and well tolerated generally. Adverse reactions are rare and drug resistance is the main problem for long-term application. Resistance can cause virological breakthrough and rebound, biochemical breakthrough and hepatitis outbreak, even liver failure and death [12]. NAs can be used for antiviral treatment in children are only some species currently. The choice is limited and the optimal treatment duration is not clear [3, 7]. The firstly approved NAs drug used for antiviral treatment in children aged over 1-year-old is LAM. The dose is 3 mg/kg•d, and the maximum is no more than 100 mg/d. But high resistance rate prevents LAM to be the preferred or long-term antiviral drugs for CHB children. It has been reported that children 52-week and extended 3-year LAM antiviral therapy were well tolerated, which had certain efficacy. But the resistance rates of 1-to-3-year duration were 19%, 49% and 19%, respectively [13]. It is usually needed at least 12 months or longer duration for NAs antiviral treatment in CHB children if there is no resistance. If HBeAg-positive children with CHB achieve virus inhibition and HBeAg seroconversion, it needs strengthen treatment of at least 6 to 12 months or longer. But the optimal duration of strengthen treatment remains unclear. HBeAg-negative children may need longer period of antiviral treatment because the recurrence rate was 70-90% in adults once stop antiviral treatment within 1-2 years. Randomized controlled clinical trials results show that oral LAM, 100 mg, once a day, can obviously inhibit HBV-DNA in adults. And HBeAg seroconversion rate increases with the prolonged treatment period. The HBeAg seroconversion rates of 1, 2, 3, 4 and 5 years treatment are 16%, 17%, 23%, 28%, and 35%, respectively, but the resistance mutation rate of virus is also increased [14]. The WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection in 2015 recommends: entecavir (ETV) can be used for antiviral treatment in CHB children over 2-year-old [10]. The experts and scholars from Europe and China recommend: tenofovir (TDF) and adefovir ester (ADV) can be used for antiviral treatment in CHB children over 12-year-old [3, 15]. Relative IFN-α contraindication of early liver cirrhosis had already appeared in these two HBeAg-positive 1-year-1-month-old children before antiviral treatment in this paper. So LAM-a NAs antiviral drug was considered. Before antiviral treatment, ALT elevated over 2ULN, HBV-DNA loads were over 105IU/ml. Antiviral therapy of LAM (3 mg/kg•d, qd, po) was administrated to them after their parents signed the informed consent. For Case 1, ALT trended to be normal at 16 weeks of treatment. HBeAg seroconversion occurred and HBV-DNA level began undetected at 24 weeks. No obvious adverse reactions were observed during the antiviral treatment. This child had been followed up for 4 years after antiviral treatment withdraw. And the ALT keeps normal, HBeAg seroconversion is maintained and HBV-DNA level sustains below the detection limit. For Case 2, ALT became normal at 24-week of treatment. HBeAg seroconversion occurred and HBV-DNA became undetected at 12-week. No obvious adverse reactions were observed during the antiviral treatment. The child had been followed up for 1.5 years after antiviral treatment withdraw. And the ALT keeps normal, HBeAg seroconversion is maintained and HBV-DNA level sustains below the detection limit.

HBV genotypes are formed from accumulation of point mutations over a long period of time. HBV mutation rate is high due to asymmetry transcription and lack of proofreading enzymes in reverse transcription. HBV genotype reflects the mutation characteristics of HBV natural infection, which is the result of virus evolution. It can be divided into different HBV genotypes according to the line of 8% HBV gene sequence heterogeneity or more. It has been identified nine genotypes A to I so far, and genotype B and C are dominant in our country [16]. The association between HBV genotype and the clinical manifestations, efficacy of treatment and prognosis is closely linked. HBeAg seroconversion rate and HBeAg seroconversion/HBsAg clearance rate after interferon antiviral therapy are higher in patient's genotype A and type B than that of C and D [3, 6, 8]. HBV genotypes of these two cases were B and C, respectively. The relationship between HBV genotype and good antiviral efficacy of LAM is yet to be explained by further study of more cases.

Children with CHB are the main source of chronic hepatitis B in China. Antiviral treatment is not usually considered due to the particularity of children's growth and development, and infants and young children are often in phase immune tolerance when they infect with HBV. According to some studies recently years, especially scientists from China with high prevalence country, they suggest that children patients with CHB should be given antiviral treatment once they enter immune clearance phase and have antiviral indications as soon as possible. Of course, it needs further long-term clinical research and more samples to conform the concrete antiviral therapy, antiviral duration, efficacy, adverse reaction and resistance, etc., for children to CHB, and to provide more evidence for guidelines for antiviral treatment of CHB children.

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