



# Infants Born to HBV Genotype A-Carrier Mothers have Begun to Appear in Japan

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## Abstract

Acute hepatitis by hepatitis B virus (HBV) genotype A causes long duration of hepatitis, and the carrier rate after acute infection is approximately 10%. The genotype A hepatitis has become the most common acute infection linked to horizontal transmission among young people in recent years. Increases in HBV genotype A-carrier mothers are expected in the near future in Japan, and prophylaxis against mother-to-child transmission for hepatitis B virus genotype A-carrier mothers will therefore be important in suppressing expansion of this viral infection. This report describes that infants born to HBV genotype A-carrier mothers have begun to appear in Japan and prevention of mother-to-child transmission (MTCT) was performed by administration of immunoglobulin derived from genotype A virus antigen with subsequent inoculation of vaccine derived from genotype C virus antigen.

**Keywords:** Hepatitis B virus genotype A; Mother-to-child transmission; HBV immunoglobulin; HBV vaccine

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## Introduction

HBV has been classified by phylogenetic analysis into 10 genotypes (A to J), based on an inter-group divergence of  $\geq 8\%$  in the complete nucleotide sequence [1-3]. Genotypes A-D account for nearly all genotypes extant in Japan, mostly as genotypes B and C. Growing evidence has recently suggested that HBV genotypes may influence hepatitis Be antigen (HBeAg) seroconversion rates, mutational patterns in the precore and core promoter regions, severity of liver disease, and response to interferon treatment. Acute hepatitis by HBV genotype A causes long duration of hepatitis, and the carrier rate after acute infection is approximately 10%, which is more likely to result in chronic infection than of other genotypes [4-7]. Accordingly, HBV genotype A hepatitis has become the most common acute infection linked to horizontal transmission among young people in recent years and the incidence of acute hepatitis caused by genotype A has been spreading in large metropolitan areas of Japan [8-10].

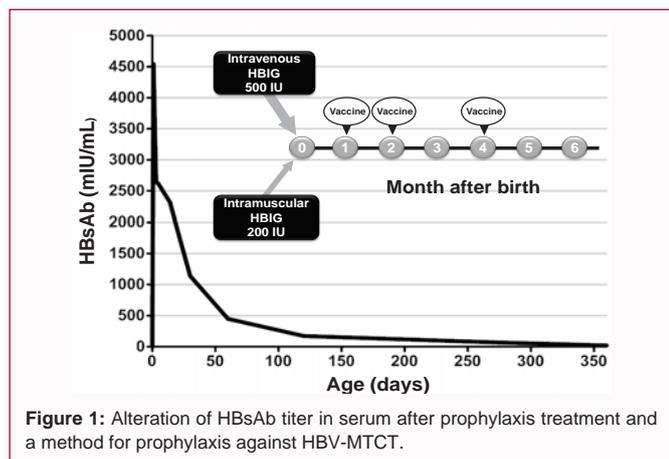
## Case Presentation

A 24-year-old pregnant woman visited to our hospital to deliver her baby in 2015. She had no symptoms and no history of hepatitis before pregnancy. Positive results for hepatitis B surface antigen (HBsAg) were identified from a blood test in the first trimester, and additional detailed examinations were performed. HBsAg and HBeAg were  $>2,000.0$  mIU/mL and negative, respectively. Hepatitis B core antibody (HBcAb) and HBsAb were 12.1 sample relative light units (RLU)/cut-off and 137.3 mIU/mL, respectively. The percentage inhibition of hepatitis Be antibody (HBeAb) was 99%. Viral load (HBV-DNA) was estimated by quantitative PCR as 4.2 log copies/mL and the genotype was A. HCV was negative, and HDV has not been analyzed on the grounds that it is extremely rare and there is no established laboratory procedure in Japan. Serum ALT and AST levels were 17 IU/L (normal, 10 IU/L to 40 IU/L) and 7 IU/L (normal, 5 IU/L to 40 IU/L), respectively. No portal inflammation and fibrosis were observed on ultrasonography. Based on these findings, we suspected acute infection shortly before or in early pregnancy, with improvement in the first trimester according to the presence of a low titer of HBcAb with a high titer of HBsAb. However, the patient also had a high titer of HBsAg and moderate viral load. We decided to monitor the course of viral load based with liver function every 3-6 weeks until delivery. Liver function remained stable during pregnancy, but no decreasing trend in the viral load was observed. Consequently, we

**Table 1:** Character of HBV for inducing immunoglobulin and providing vaccine.

		Product Name	Vaccine for inducing immunoglobulin	Genotype	Phenotype
HBIG	Intravenous	Hebsbulin IH IV (Japan Blood Products Organization)	Engerix-B® (GlaxoSmithKline)	A2	adw
	Intramuscular	Hebsbulin IM (Japan Blood Products Organization)	Engerix-B® (GlaxoSmithKline)	A2	adw
Vaccine		Bimmugen® (The Chemo-Sero-Therapeutic Research Institute)	-	C	adr

HBIG: Hepatitis B virus immunoglobulin



**Figure 1:** Alteration of HBsAb titer in serum after prophylaxis treatment and a method for prophylaxis against HBV-MTCT.

considered that she was unlikely to improve during pregnancy and the risk of MTCT was thought to be high, and we concluded that prophylaxis treatments were required for baby. The patient delivered a 2,738 g boy vaginally at 39 weeks and 4 days of gestation without any complications. Infant Apgar scores were 8 at 1 min and 9 at 5 min.

Hepatitis B virus immunoglobulin (HBIG) was simultaneously administered to the neonate both intravenously and intramuscularly within 12 h after birth [11] (Figure 1). Drug doses were 500 units for intravenous HBIG (Hebsbulin IH, IV; Japan Blood Products Organization, Tokyo, Japan) and 200 units for intramuscular HBIG (Hebsbulin IM; Japan Blood Products Organization). Vaccination (Bimmugen; The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) was started 1 month after birth and subsequent additional shots were administered at 2 and 4 months of age. We followed up the mother and her baby for over a year. Although direct nursing was continued during the lactation period, the baby did not show serological HBV infection at 1 year of age. The mother provided written consent to participate in this study and for analysis of blood samples. Treatment was approved by the ethics committee of our institution (No. 532, Jan 6, 2012).

**Discussion**

HBV genotype A shows atypical progression of stages after infection and the difficulty of diagnosis will represent a problem when deciding of preventive methods of MTCT. Viral load offers an obvious parameter for gauging viral activity in the body, regardless of Ab types and titers, and occasionally an overwhelming amount of HBsAb is needed for prevention on the ground that many viruses can remain despite a high titer of HBsAb in the bloodstream. This case showed a median viral load in spite of being HBsAb, taking the existence of the mutant into account; we decided to implement prophylaxis protocol using administration of HBIG [11] and subsequent vaccination. With the aim of achieving greater prevention of MTCT of HBV, comprising intravenous administration along with

ordinary intramuscular administration of HBIG, to be administered to the neonate shortly after birth. After taking into consideration the risks of the mother taking antivirals before delivery, we selected this combined HBIG method, which is safe for babies [11] and does not require antiviral control of maternal viral load during the perinatal period [12]. In addition, treatments for infected babies are restricted by the safety and efficacy of antiviral drugs. Vaccination was started 1 month after birth with additional 2 shots during lactation. More than 10 IU/mL of the HBs antibody has been kept for 1 year after birth and the baby was protected from the HBV infection.

The HBIG for both intravenous and intramuscular injection is refined from a serum pool obtained from the human immunized genotype A HBV antigen [13-15], while vaccine antigen was derived from that of genotype C HBV antigen (Table 1). Phenotype of the HBs antigen, especially “a” antigen, should be conserved in HBV even if genotypes are different [13-15] and antibodies to the “a” antigen have neutralizing activity against any genotypes. We performed prevention of mother-to-child transmission (MTCT) by administration of immunoglobulin derived from genotype A virus antigen with subsequent inoculation of vaccine derived from genotype C virus antigen.

It is expected that increasing HBV carrier rate of mother with genotype A near future in Japan and prophylaxis against MTCT in genotype A HBV carrier mothers will be especially important to suppress expanding the viral infection.

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