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Letter to the Editor Open Access

Human Bocavirus DNA Tested in Cord Blood of a Newborn with Hydrop

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Since its initial detection in 2005 [1], human bocavirus (HBoV) were reported to be able to infect human by respiratory and gastrointestinal pathway worldwide [2]. Recently, mounting evidences suggested that HBoV was apt to co-infect with other viruses and only cause mild clinical signs [3-5]. But our previous study observed a direct correlation of high viral load with increasing disease severity in children (under 5 years of age) with respiratory illness [6]. HBoV may play an important role in disease progression in infants with severe respiratory infection. HBoV is classified in the family Parvoviridae. Parvovirus B19 (B19) and human parvovirus 4 (PARV4) are two other important members of Parvoviridae which can cause human infection. As the first human related parvovirus, B19 has been recognized as the cause of fetal hydrops and death [7]. Similarly, the DNA of PARV4, another newly defined human parvovirus, was detected in plasma of a newborn with hydrop in Taiwan recently [8]. HBoV may share similar properties with its relatives, such as the capability of spreading by placenta. To address this issue, a study tested HBoV DNA in formalin-fixed paraffin-embedded fetal tissues [9], the other detected HBoV DNA in amniotic fluid samples from fetuses [10]. Both studies reported negative results. Formalin fix may influence the nucleic acid in samples and inappropriate samples used in the above studies might result in the negative results.

To ensure the quality of samples, fresh paired maternal and cord blood samples from 65 abnormal growth newborns were collected and the presence of HBoV DNA in those blood samples were assayed using specific HBoV primers. The amplification products were retrieved and sequenced with specific HBoV sequencing primers. Our results may help to further elucidate the transmission route of HBoV.

Our study conducted in the second affiliated hospital of Wenzhou Medical College. From July 2012 to March 2013, a total of 65 abnormal growth newborns, including 17 intrauterine growth restriction (IUGR) newborns, 33 LBW (low birth weight) newborns, 15 macrosomic newborns and their mothers were enrolled in our study. All subjects signed written informed consents approved by Fudan University's Institutional Review Board. Maternal blood, cord blood and placental samples were collected immediately after delivery. The demographic characteristics of newborns, including birth weight, birth length, and gestational age, etc. were obtained from hospital records.

Sera were isolated from all 130 blood samples within 6 hours post collection in the clinical laboratory of the above hospital and sent to Shanghai Municipal Center for Disease Control and Prevention (SCDC). Total nucleic acid of each sample (200 μl) was isolated by the MagNA Pure LC 2.0 (Roche, Switzerland) using MagNA Pure LC DNA Isolation Kit (Roche, Germany) following manufacturer's recommendations. For quality control, besides assay HBoV DNA, we also detected DNA of the more common viruses HBV and B19 which were known to cause vertical transmission more frequently from infected mother to their infants. HBoV, B19 and HBV DNA were detected in all samples using commercial real time PCR kit "Shanghai Z.J. Bio-Tech Co., Ltd., People's Republic of China" using Roche Light Cycler 480 (Roche, Switzerland).

HBoV DNA was tested in 1 cord blood sample and none of the maternal blood, see Table 1. To further confirm our results, the amplification product of the HBoV DNA was retrieved, purified and sequenced using a set of specific HBoV primers. Then the sequence was blasted in Genbank. The blast result showed that the identity ratio is of 100% between the sequence which we detected in cord blood of a newborn and the HBoV strain Irish, complete genome (Sequence ID is "gb|KC823115.1, see Figure 1. Our result suggested that HBoV probably passed through the placenta barrier of the newborn. Previous studies [9,10] did not detect HBoV in fetal tissues or amniotic fluid samples from fetuses. Their negative results may due to the quality of their samples. In this study, we did not detect HBoV DNA in the maternal blood of the pair-case whose cord blood is positive. Our result is in consistent with observation from a newly published paper that the prevalence of HBoV DNA in adult female individuals is rare (1.4%) in china [11]. Besides HBoV DNA, B19 DNA was also assayed in the same infants with HBoV DNA, see Table 1. It is reported that HBoV always co-infected with a second pathogen and can persist for an extended period of time [12]. It is interesting that totally 4 cord blood showed positive results to B19 DNA detection but none of their paired maternal blood were positive to B19 DNA. Therefore, it is possible that, after co-infected with B19 and HBoV, the two viruses might transiently emerge in maternal blood and then passed placenta barrier and persisted there. B19 has been observed to be able to pass the placenta and cause of fetal hydrops and death [7]. In the current study, 6.2% (4/65) of infants could have been infected by B19 through placenta transmission and 3 of them were low birth weight and one was Macrosomia. Our results confirm that B19 is apt to spread from mother to baby.

HBV DNA was tested positive in 4 of the 65 maternal blood samples and 1 of the 65 cord blood, see Table 1. HBV DNA presented in the cord blood of an newborns whose mother was among the 4 mothers with HBV DNA positive detection results in their blood samples. Therefore, HBV DNA prevalence in the newborn mothers is 6.2% (4/65), and the vertical transmission rate is 1.5% (1/65). Besides, 1 out of 4 HBV infected pregnant women could transmit HBV to their babies. Our result matches the observations from a national multi-stage

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Infants ID	1	2	3	4	5	6	7	8
B]19 in Cord blood	-	-	+	+	-	+	-	+
B19 in Maternal blood	-	-	-	-	-	-	-	-
HBoV in Cord blood	-	-	-	-	-	+	-	-
HBoV in Maternal blood	-	-	-	-	-	-	-	-
HBV in Cord blood	+	-	-	-	-	-	-	-
HBV in Maternal blood	+	+	-	-	+	-	+	-
Status	IUGR	LBW	LBW	LBW	LBW	LBW	LBW	Macrosomia
Sex	Female	Male	Female	Female	Female	Female	Male	Male
Delivery	CS	CS	Vaginal	CS	CS	Vaginal	Vaginal	CS
Birth weight(kg)	1.78	2.17	2.23	2.07	2.38	2.27	2.36	4.2
Birth length(cm)	42	49	48	45	45	46	47	52
Gestational age(week)	35.7	33.9	33.7	34.7	35.6	35.4	34.1	39
Pregnancy complications	Yes	Yes	Yes	Yes	Yes	No	No	Yes

Table 1: The Clinical Information, as Well as Test Results of B19, HBoV and HBV DNA in Paired Blood Collected from 8 Infants.

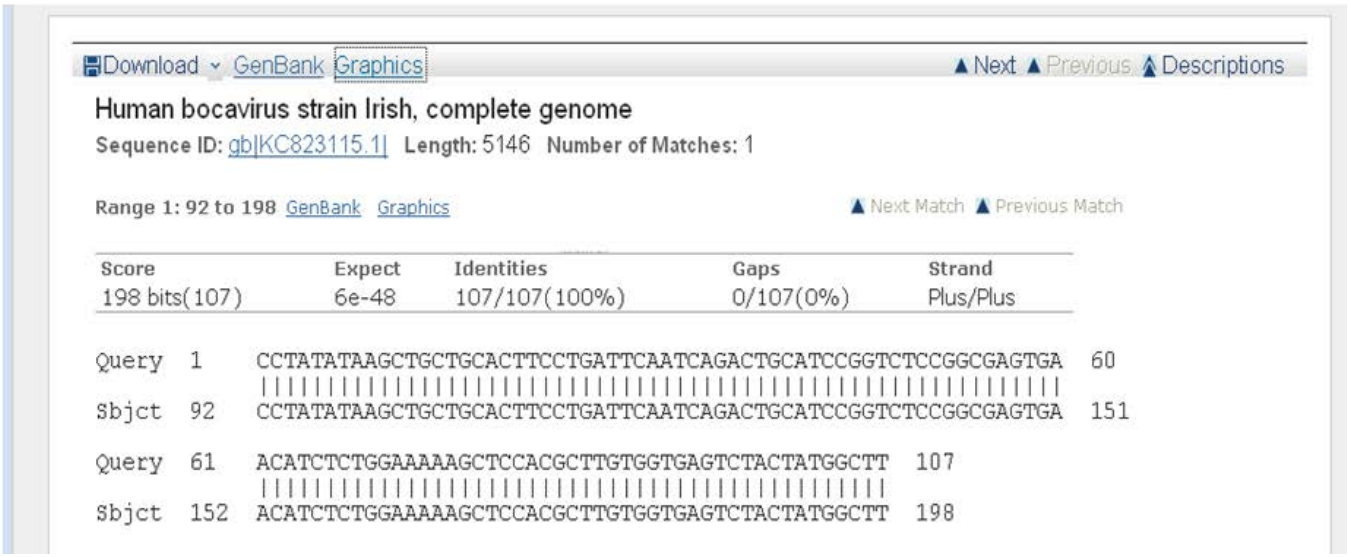

Figure 1: The blasting results matrix from GenBank between the HBoV sequence which we detected and the HBoV strain Irish, complete genome (Sequence ID is GB|kc823115.1|).Total nucleic acid of each sample (200 µl) was isolated by the MagNA Pure L.C. 2.0 (Roche, Switzerland) using MagNA Pure LC DNA Isolation Kit (Roche, Germany) following manufacturer's recommendations. HBoV DNA were detected in all samples using commercial real time PCR kit ("Shanghai ZJ Bio-Tech Co"., Ltd., People's Republic of China) using Roche Light Cycler 480 (Roche, SwitzerlandT). Then the amplification product was retrieved, purified and sequenced using a set of specific HBoV primers. Then the sequence was blasted in Genbank. The blast matrix from Genbank were downloaded with the identity ratio between the sequence which we detected in cord blood of a newborn and the HBoV strain Irish, complete genome (Sequence ID is "gB|kc823115.1|" displayed.

random sampling sero-survey in China [13], as well as a population-based study from Gansu province of China [14] that, 7.2% of Chinese population aged ≥1 year old showed positive results for HBsAg assay. As the blood samples are limited, we did not detect serological mark of HBV infection. The results suggested that our laboratory detection results are qualified.

In the current study, we detected HBoV DNA in one cord blood sample. The sequence analysis shows that it is a genotype 1 HBoV. Our results suggested that HBoV might pass through the placenta barrier and resulted in birth complications in infants. To our knowledge, it is the first study to provide evidence for HBoV vertical transmission.

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