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CASE REPORT

De novo HBV Hepatitis in a Child with Liver Transplantation

Ioannis XINIAS[a], Konstantina VASILAKI[a], Evangelia ARGIROPOULOU[a], Antigoni MAVROUDI[a], Olga TSIATSIOU[b], Emmanouel ROILIDES[b]

[a]Aristotle University of Thessaloniki, Third Paediatric Department, Gastroenterology Unit, Hippokration Hospital, Thessaloniki, Greece

[b]Aristotle University of Thessaloniki, Third Paediatric Department, Infectious Unit, Hippokration Hospital, Thessaloniki, Greece

ABSTRACT

Background: *HBV infection is rare in developed countries due to global immunisation. However, children with immunosuppression such as organ transplantation are at a higher risk to develop HBV hepatitis. Our goal is to highlight the risk of children with liver transplantation developing* de novo *hepatitis B although they were immunised with the HBV vaccine, and have seroprotective antibody titers.*

Case report: We report about a female toddler with liver transplantation due to extrahepatic biliary atresia, who was detected to have positive HBsAg, 27 months after transplantation. Before liver transplantation, routine serologic assessments were negative for HBV infection, the child was vaccinated with three doses of HBV vaccine and developed seroprotective Abs titers. Organ donor was the father, who was negative for HBV infection had negative anti-HBc and had seroprotective titers of anti HBs.

A PCR assay in our patient revealed the presence of serum HBV DNA with an increased viral load. The patient started antiviral treatment with Entecavir and had serological response within three months, showing elimination of serum HBV DNA and HBsAg values. Serological investigation of all family members and information from the transplantation unit did not reveal the infection source.

Conclusion: de novo *Hepatitis B in liver recipients is a rare phenomenon. In donor positive anti-HBc cases, it appears as reactivation of HBV infection. There are very few published cases in which recipients developed* de novo *HBV hepatitis, despite seronegative HBcAb donors. Caregivers should always be alert for* de novo *hepatitis B in liver transplanted children as loss of immunity could be an unexpected phenomenon, despite pre-transplant negative serology of the donor and recipient as so as despite seroprotective Abs titers after immunisation of the recipient.*

Keywords: liver transplantation, *de novo* hepatitis B, children.

Address for correspondence:
Ioannis Xinias
Konstantinoupoleos 49, 56642 Hippokration Hospital, Thessaloniki, Greece
Tel. +302310992877; Email: xinias@email.com

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INTRODUCTION

Hepatitis B infection is a severe cause of morbidity and mortality from hepatic illness globally. About 90% of adult patients, 70% of children and just 10% of neonates achieve spontaneous viral clearance after acute HBV infection in six months. The rest of the patients do not have the ability to clear the virus and develop chronic disease (1). HBV infection in developed countries is a rare phenomenon due to global immunisation. However, children with immunosuppression such as liver recipients are at a higher risk to develop HBV infection.

All children who are candidates for solid organ transplantation have to get three doses of HBV vaccine prior to transplantation and to be periodically checked for sufficient antibody titers after transplantation. Moreover, in living donor transplantation cases, the donor must be checked thoroughly for HBV infection and protection status (2).

The goal of our report is to highlight the particularity of children with liver transplantation and their risk to develop *de novo* hepatitis B, although they were immunised with the HBV vaccine, and developed seroprotective antibody titers. ❑

CASE REPORT

A female toddler diagnosed with extrahepatic biliary atresia at the age of two months underwent an initially unsuccessful Kasai porto-enterostomy procedure. At the age of 15 months, the patient received a liver transplant due to deterioration of her liver function. The donor was her father, who was negative for HBV infection in the pre-transplant period and had seroprotective HBV antibodies (79 mIU/mL) and negative HBsAg (0.05 S/CO), anti-HBc (0.00 S/CO) and HBV-DNA (undetectable copies/mL). He had received full hepatitis B vaccination in childhood and anti HBc was not tested till the last months because there was no medical reason for this.

During the pre-transplant period, the child had a routine (every four months) clinical and laboratory assessments such as HBsAg (0.05 S/CO), anti-HBs (0.04 S/CO), anti-HBc (total 0.09 S/CO), HBV-DNA (0.0 copies/mL).

She had received three doses of HBV vaccination before transplantation (at the second, fourth and eighth month of life) and HBV serology was indicative for immunity through HBV vaccination (anti-HBs: 1800 mIU/mL, HBs DNA: 0.0 copies/mL, HBsAg: 0.03 S/CO, total anti-HBc: 0.09 S/CO).

Two months after liver transplantation, the toddler had a CMV infection documented by PCR, successfully managed with iv gancyclovir.

Three months later, the child manifested an acute episode of cholangitis. Laboratory investigation with cholangiography and liver biopsy revealed progressive stenosis of the biliary anastomosis and mild liver rejection. Fourteen months later, a procedure of biliary dilatations in the anastomotic areas was successfully done.

Routine serology testing revealed positive HBsAg, In addition, HBeAg and anti-HBs were also positive (Table 1). At this time, liver enzymes were normal but showed elevated levels a couple of months later (Table 2).

A following HBV-DNA PCR revealed a viral serum load of 3.6×10^6 copies/mL (Table 1).

Upon confirmation of HBV infection, antiviral treatment with entecavir was started.

Serum laboratory values	Pretransplant	At the time of *de novo* HB diagnosis	One month later (starting entecavir treatment)	Six months later	Normal value	Units
HBsAg	*0,07*	*48,60*	*5658,27*	0.85	0,00 - 1,00	S/CO
Anti-HBs	*115,78*	*93,76*	*151,93*	139.45	0,00 - 10,00	mIU/mL
HBeAg	Negative	Negative	*Positive*	Negative	0,00 - 1,00	S/CO
Anti-HBe	Negative	Positive	Positive	-	>1,00	S/CO
Anti-HBc-Total	Negative	Negative	Negative	Positive	0,00 - 1,00	S/CO
Anti-HBc-IgM	Negative	Negative	Negative	-	0,00 - 1,00	S/CO
HBV DNA – PCR	Negative		*3,6 X 10^6*	*Negative*		copies/mL

TABLE 1. HBV serum markers in our patient before and at the time of diagnosis, and after treatment

	Six months before diagnosis	At the time of *de novo* Hep B diagnosis	Three months later	Four months later	Six months later	Normal values
SGOT (mg/dL)	114	40	257	66	51	5-40
SGPT (mg/dL)	96	33	458	42	39	5-37
g-GT (U/L)	192	308	164	92	81	5-60
Alkaline phosphatase (U/L)	458	264	458	458	399	81-293
Lactic dehydrogenase (U/L)	677	261	347	407	398	201-598
Serum proteins (g/dL)	8.4	7.9	8.0	7.2	7.4	5.5-7.8
Serum albumin (g/dL)	3.9	3.9	3.7	3.6	3.8	3.5-5.0
Total bilirubin (mg/dL)	1.45	0.57	1.48	0.68	-	0.4-1.2
Direct bilirubin (mg/dL)	0.86	0.19	0.94	0.26	-	0.3-0.8

TABLE 2. Patient's biochemistry values before and after HBV diagnosis and treatment

The response of our patient was satisfying after three months of follow up, showing elimination of serum HBV DNA (2.1 X 106 copies/mL) and HBsAg values (2531.21 S/CO) and elevation of anti-HBs (121.22 S/CO).

The child had no symptoms and blood biochemistry showed an elevation of liver enzymes at the follow-up.

Six months after treatment, HBV DNA was undetectable and liver enzymes were normal (Table 1).

A thorough investigation was conducted for the identification of the source transmission. The investigation included assessment of transmission *via* the donor, transmission after blood transfusions, *via* surgical and technical procedures and last about an intra-familial way of transmission.

No sequencing of the viral strain has been performed to identify any escape mutations because there was no laboratory support for such an investigation.

The donor was negative for HBV DNA before and several months after the transplantation procedure.

Moreover, the patient had seroprotective titers of anti-HBs (>1 000 IU/mL) before transplantation as well as a few weeks before the diagnosis of *de novo* hepatitis B.

Blood transfusions could be a reason for HBV transmission, but our patient had a minimum of transfusions (1-2) and strength measures according to the international protocols for transfusions were followed. ❑

DISCUSSION

HBV vaccine represents the most effective way to prevent HBV infection (3, 4). For healthy children, routine anti-HBs testing after standard HBV vaccination and booster doses are not recommended.

For immunocompromised people (*e.g.*, those receiving immune suppressive therapies such as calcineurin inhibitors), the need for booster doses has not been determined. However, annual anti-HBs testing and booster doses when anti-HBs concentrations decrease to <10 mIU/mL should be considered if they have an ongoing risk for HBV exposure (5-7).

In recipients receiving liver grafts from anti-HBc positive donors, robust strategies have been developed to prevent viral activation and *de novo* hepatitis B infection. These strategies involve passive immunisation with hyperimmune hepatitis B immunoglobulin (HBIG), with or without an antiviral agent, or the hepatitis B vaccine (7-10).

Prevention of *de novo* hepatitis B infection in recipients of tissue from anti-HBc negative donors has generally been disregarded because evidence to support *de novo* hepatitis B infection from the loss of HBV immunity after liver transplantation is scarce (11, 12).

Reviewing past and current bibliography, a very few similar cases who developed *de novo* HBV hepatitis were reported in liver recipients who were seronegative for HBsAg. However,

these pediatric cases received a liver graft from HBsAg negative and anti-HBc positive donors (7-10).

In patients with HBsAg and anti-HBc negative donors before liver transplantation, the loss of recipient's HBV immunity post-transplant is scarce (11, 12). Some data support the hypothesis that the loss of seroprotective HBV abs titers is an unexpectedly common phenomenon in immunosuppressed patients (6). Therefore, we could conclude that high anti-HBs serum titers (>1000 IU/L) are not protective against *de novo* hepatitis B. Our case shows that this could be a real phenomenon and that *de novo* hepatitis could appear in seronegative liver recipients who receive grafts from seronegative and anti Hbc negative donors. These patients may have already three doses of HBV vaccine pre-transplant (13-15).

Moreover, we thought that our patient had simultaneous positivity for both HbsAg and HbsAb, an uncommon phenomenon, and considered that this could be explained by the fact that she had an impaired immune system due to immunosuppression. ❑

CONCLUSION

Regular assessment of anti-HBs titers after liver transplantation should be considered in liver recipients along with revaccination to prevent HBV infection. However, caregivers should be alert for *de novo* hepatitis B appearance since this could be an unexpected phenomenon in liver transplanted children, despite negative serology and protective antibody titers. ❑

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