

## Research Article

# Low Birth Weight is a Predisposing Factor for the Liver Tumors?

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**Abstract**

**Purpose:** The most common types of liver tumors in pediatric patients are hepatoblastoma (HBL) and hepatocellular carcinoma (HCC). The relationship between perinatal characteristics and hepatoblastoma as well as the outcome of liver tumors is the aim of our study.

**Methods:** 11 children with liver tumors who were diagnosed and treated in our unit were enrolled in our study. The age at diagnosis ranged from 2 months to 5 years for HBL (med:12 months) and 7-8 years for HCC. Predisposing factors such as hepatitis B,C, CMV, or metabolic disorders were tested. All patients treated according to SIOPEL protocol (plus Nexavare, in HCC) and remain in remission.

**Results:** 9 cases had HB and 2 HCC. The birth weight of patients was ranged from 1770gr-3850gr while 6 out of eleven children (66%) had birth weight lower than 2900gr. The gestational age in 4 cases was up to 37 weeks. Predisposing factors were not observed in any of our cases. All cases are in complete first remission. One patient with HCC had reactivation of the disease but achieved remission after second surgery.

**Conclusion:** 1) There is an increased risk for hepatoblastoma among children with low birth weight. 2) No predisposing factors were found in children with HCC. 3) Although the HCC is usually diagnosed at the age of 10-14 years old, our cases were diagnosed in the earlier childhood. 4) Surgical resection and the SIOPEL protocol give an excellent outcome, without radiotherapy.

**ABBREVIATIONS**

**HBL:** Hepatoblastoma; **HCC:** Hepatocellular Carcinoma; **SIOPEL:** International Society of Pediatric Oncology on Childhood Liver Tumors; **COG:** Children's Oncology Group; **LBW:** Low Birth Weight; **VLBW:** Very Low Birth Weight; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus; **MCV:** Cytomegalovirus

**INTRODUCTION**

The primary malignant liver tumors represent approximately 1.1% of tumors of childhood. The annual incidence in the USA is 1.8 cases per million children, in Europe the incidence appears to be slightly higher. Hepatoblastoma (HBL) is the most common type of malignant liver tumor in children, comprising approximately 1% of malignant neoplasms among children and followed by hepatocellular carcinoma (HCC) (approximately

0,5%) [1, 2]. Hepatoblastoma is mainly a tumor occurring in early childhood. The 30-50% of the HBL cases occurs in the first year of life and the 90% before the age of 5 years. The onset peak of HCC is in older age than that of HBL in childhood. Lee, et al. reported that there is an HCC onset peak at the age of 10-14 years [3,4]. As the hepatoblastoma is a malignancy in early childhood and its moderately differentiated histology suggests developmental origin, special attention has been given to gestational and birth characteristics. The most striking and consistent association has been a strong inverse relationship between birth weight and hepatoblastoma risk [5]. An analysis of Japanese cancer registry data revealed an increasing trend in hepatoblastoma incidence among children of very low birth weight [6]. Because perinatal medicine has rapidly progressed and its services have become standard, the survival of children with low birth weights has increased recently. There is not yet answered if hepatoblastoma

that developed in fetal life is detected because of improved survival of low birth weight infants or hepatoblastoma tend to occur in children with a very low birth weight. Male gender is associated with hepatoblastoma risk. In Europe the proportion of boys:girls is about 2.1:1[7]. Regarding to the treatment of liver tumors surgical removal of the tumor either as initial treatment or after chemotherapy is the basis and purpose of the treatment. Hepatoblastoma is more chemo sensitive than hepatocellular carcinoma. More than 70% of HCC are considered unresectable at the time of diagnosis. Combination chemotherapy has been used to patients with HCC but has been largely ineffective in shrinking the tumor to the point of respectability and in eradicating metastases. In cases where the tumor seems unresectable due to anatomical reasons or after preoperative chemotherapy, criteria have been developed so that patients undergo timely liver transplant after brief chemotherapy [8-12]. The aim of the study was the demographic and birth characteristics of malignant liver tumor of our center and the outcome.

## MATERIALS AND METHODS

All consecutive children who were diagnosed in the Hematology/Oncology Unit in the 1<sup>st</sup> Dept of Pediatrics of Athens University with malignant liver tumor in the last decade were included in this study. No patient excluded of this prospective study. All patients diagnosed and treated in our unit.

### Study design

Clinical data providing demographic information, pregnancy history, and childrens' birth characteristics are included in the study. Diagnosis was confirmed by histological analysis. Laboratory evaluation for underlying disease was performed in all patients. Cases with HCC were laboratory examined for Hepatitis, Wilson disease, autoimmune diseases of the liver and metabolic diseases, using the standard methods for these diseases. All patients were treated according to SIOPEL protocol plus Nexavare, in HCC patients. All patients had a routine follow up, till recently. This study was approved by the ethical committee of Athens University.

## RESULTS AND DISCUSSION

### Results

Eleven children were enrolled in this study, 9 cases with hepatoblastoma and 2 with hepatocellular carcinoma. Liver tumors incidence appeared slightly higher in males than in females, with a ratio of 1.20:1. The age at diagnosis ranged from 2 months to 8 years with median age in all cases was 2<sup>10/12</sup> years. The age at diagnosis for HBL ranged from 2 months to 5 years while the 56% of the diagnoses occurred the first year of life. The age of diagnosis for HCC was 7 and 8 years respectively. The birth weight of all patients ranged from 1770gr-3850gr while 6 out of nine cases (66%) with HBL had birth weight lower than 2900gr. The gestational age in 4 out of 11 cases was up to 37 weeks. All cases had no other predisposing factors such as hepatitis, Wilson disease, autoimmune disease of the liver or metabolic disease. All our patients had a total resection of tumor. In two cases there was a total resection of the tumor at diagnosis followed by chemotherapy while the other nine cases received preoperative chemotherapy. All cases except one are in complete

first remission. One patient with HCC had reactivation of the disease but achieved remission after second surgery. All patients remain in remission.

### Discussion

An increase incidence of hepatoblastoma, was observed in last decade coinciding with improve survival rate for infants with low birth weight. It confirmed also by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program [13]. The 81% of our patients could be considered as term babies "full- or early-term", but most of them have a relatively low birth weight for their gestational age (<2.900gr) (Table 1). The relative risk for hepatoblastoma increases inversely with birth weight. In children with birth weight less than 1.000g, hepatoblastoma risk is 15 times greater than that in infants with normal birth weight [7, 14-16]. Tanimura M. et al. reported that this occurs due to the extremely sensitive liver prematurity which has not been developed enough as well as due to the risks faced by infants in perinatal treatment. However, the question that arises is the relation between hepatoblastoma and the factors that are responsible for low birth weight infants. It is known that inflammation of mother, nutrition and prenatal care are some of the main causes for babies "small for date". It is known that endotoxins that released in an inflammation can actually get into the bloodstream and target the fetus, potentially leading to premature labor and low-birth-weight infants [17]. Could these factors predispose to hepatoblastoma in low birth weight infants? It seems that the etiology of the development of hepatoblastoma differs between patients with very low birth weight <1000gr and normal weight patients [16]. The Children's Oncology Group (COG) through the treatment protocol for hepatoblastoma (AEP104C1) investigated retrospectively (2000-2005) and prospectively (2005-2008) the etiology factors of the development of hepatoblastoma in low (low birth weight, LBW) and very low birth weight (VLBW) preterm infants) and is the largest study to date (case-control study) designed for the causes of hepatoblastoma. The incidence of HBL is higher in full term babies with lower birth weight than full term babies with

**Table 1:** Diagnosis and Birth characteristics.

Cases/ Date at Diagnosis	Gender	Diagnosis	Gestational age (weeks)	Birth Weight
1/ 4 years	Female	Hepatoblastoma	38w	2550gr
2/9 months	Male	Hepatoblastoma	40w	4000gr
3/5 years	Male	Hepatoblastoma	36w	2450gr
4/3 months	Male	Hepatoblastoma	37w	2900gr
5/2 months	Female	Hepatoblastoma	38w	3450gr
6/2 years	Female	Hepatoblastoma	38w	3250gr
7/1 year	Female	Hepatoblastoma	39w	2800gr
8/2 years	Male	Hepatoblastoma	40w	3850gr
9/8 years	Male	Hepatocellular carcinoma	37w	2676gr
10/7 years	Male	Hepatocellular carcinoma	39w	3680gr
11/10 months	Female	Hepatoblastoma	32w	1770gr

normal birth weight. The screening with abdominal ultra sounds in the first year of life in children with birth weight under the 2900gr could be an indication for the early detection of the disease. It is also observed a trend toward decreasing incidence during subsequent years of life. In our study, there was also an increased occurrence (56%) of the HBL in the first year of life. Regarding to HCC cases, it is remarkable that the age of diagnosis in our two cases was 7 and 8 years old respectively. Although the HCC is usually diagnosed at the age of 10-14 years old, our cases were diagnosed earlier in childhood. This point creates a thought of a decrease in the age of diagnosis in pediatric HCC. The liver dysfunction is the main predisposing condition (HBV, HCV) for the hepatocellular carcinoma. The pathophysiology is not well understood. Hepatocellular carcinoma can also develop in a background of inherited metabolic disease. In our study, cases with HCC had no hepatitis or inherited metabolic disease as predisposing factors.

All our patients remain in remission after surgically resection of the tumor and chemotherapy. Complete surgical resection remains the goal of current therapy for HBL for cure. Two main strategies for approaching resection of the tumor are noted. In the United States, the bias is towards early resection of tumor at diagnosis. Proponents of this therapy argue that the cumulative toxicity of chemotherapy can be reduced. Some agents also, can be entirely avoided, and a reduction of in vivo development of tumor resistance may also occur. An opportunity to delay resection until after neoadjuvant therapy is observed in patients with stage III and IV tumors. Future COG protocols plan to introduce a risk based determination of treatment, with low, intermediate, and high risk categories. These categories will also aid in follow up and prognosis. The identification and development of new prognostic stratifications has led to novel treatments for high-risk patients and to avoid the delayed effects and unnecessary toxicities associated with treatment. In contrast, the SIOPEL group advocates neoadjuvant therapy in all patients. They argue that primary systemic chemotherapy may reduce the size of the tumor and may allow for easier complete resection and lower morbidity. They also argue that the toxicity of chemotherapy is offset by the high rates of complete excision [18]. Recently, international collaboration study should be required for prompt clinical trials. CHIC (Children's Hepatic Tumors International Collaboration) was formed to focus on international global cooperation for investigations of pediatric malignant hepatic tumors, including HBL. The leading multicenter groups in CHIC are JPLT (Japanese Study Group for Pediatric Liver Tumors), SIOPEL, GPOH (German Paediatric Oncology and Haematology Society) and COG [19-21]. In patients with tumors that do not adequately respond to resection, orthotopic liver transplantation is an option if no evidence of regional or distant metastases is noted or when that metastatic disease has been surgically removed [9]. Hepatoblastoma can be completely removed at diagnosis in 30% of cases. Local disease has the 60% of patients with HBL, but it is not possible to give radical removal of the tumor. 10% of patients have already metastasized at diagnosis, usually the lungs. Patients with HBL appeared to have better survival compared with patients with HCC, and there was significant improvement in the disease specific survival of children treated in the recent decade [12, 22]. In HCC complete

surgical resection or transplantation is often the only chance for cure because of their poor response to chemotherapy [23]. Recently, the use of sorafenib (Nexavar), a novel tyrosine kinase inhibitor of angiogenesis, has shown some benefit in clinical trials and has been approved for HCC in adults by the USA Food and Drug Administration (FDA) [24]. Schmidt et al. also support in their recent study that sorafenib in combination with PLADO (Cisplatin/Doxorubicin) may be a promising approach in pediatric HCC. Due to this study, our patients received PLADO and Nexavar. In combination with the surgical treatment they had an excellent outcome. In our study the 82% of cases received preoperative chemotherapy. Two out of 11 patients, one with HB and one with HCC had a total resection at diagnosis. The patient with HCC had reactivation of the disease but achieved remission after second surgery. One case with HBL had a liver transplantation (data are not shown). For future therapies of HBL Bcl2 appears to play a role in the antiapoptotic mechanisms of some hepatoblastoma (HBL) subtypes. This gene may serve as a target for future gene directed therapy. The Wnt signaling and mutations in the betacatenin gene have been shown to be present in HBL specimens. A better understanding of these pathways may lead to targeted therapies [25,26].

## CONCLUSION

1) Our study enhances previously reported findings of an increased risk of hepatoblastoma among children with low birth weight. A routine ultrasound scan is highly recommended to babies of this subgroup even in full term infants for the early detection of the disease. 2) No predisposing factors were found in children with HCC. 3) Although the HCC is usually diagnosed at the age of 10-14 years old, our cases were diagnosed in the earlier childhood. 4) The new treatment strategies, lead to the excellent outcome of liver tumors in childhood without radiotherapy.

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