What do we know about the etiology of hepatoblastoma?

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“The time is ripe to move the hepatoblastoma research agenda beyond simple associations and to move toward understanding the genetic underpinnings of this challenging childhood malignancy.”

Hepatoblastoma (HB) is a rare hepatic tumor of early childhood with unclear etiology. Associations with inherited syndromes, as well as with parental exposures, have been reported, but these account for only a small number of cases. A strong association with low birth weight (LBW; <2500 g) has been identified, suggesting a potential genetic link. To date, the rarity of HB has made understanding its genetic underpinnings challenging; however, recent successful genome-wide association studies in the settings of rare tumors are encouraging and have set the stage for potential exciting discoveries in HB [1].

Epidemiology: rare, but on the rise

HB represents approximately 1% of malignancies in children 0–19 years of age. It is the most common hepatic malignancy of childhood and has steadily increased in incidence over the last three decades, with a 5% annual increase between 1973 and 1992, and a 4% annual increase between 1992 and 2004 [2,3]. Between 2006 and 2010, according to the US Surveillance, Epidemiology and End Results data,

incidence rates were 9.4 cases per million children <1 year of age and 5.5 cases per million children 1–4 years of age, with markedly reduced rates beyond the age of 5 years [101]; there is a slight male predominance [4]. The 5-year relative survival in the USA is currently 78% [101].

Etiology: syndromes, surroundings & size

■ Inherited syndromes & congenital anomalies

Although generally sporadic, HB has been associated with several inherited syndromes, which account for up to 15% of cases [5]. The most frequently associated syndromes include Beckwith–Wiedemann syndrome (BWS) [6], familial adenomatous polyposis [7] and trisomy 18 [8]. BWS is an overgrowth disorder associated with a predisposition to development of embryonal tumors early in life, including Wilms' tumor, HB, neuroblastoma and adrenocortical carcinoma. Among individuals with BWS, the relative risk of developing HB by the age of 4 years is 2280 [6]. The underlying genetic alterations that are most

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strongly associated with development of malignancy in BWS include disordered imprinting within *H19* and *IGF2*, as well as paternal uniparental disomy at 11p15.5 [9]. Familial adenomatous polyposis is characterized by the development of numerous colonic polyps with eventual progression to colon cancer by early adulthood. It is the result of inactivating mutations in the *APC* gene and HB is a rare outcome in affected individuals [10]. The relative risk of developing HB by 4 years of age among individuals with familial adenomatous polyposis is 846 [7]. Trisomy 18 is a syndrome associated with multiple congenital anomalies. There have been several case reports of HB in children with trisomy 18 [8,11,12]; however, given the rarity of the two disorders and the short life expectancy in trisomy 18, the relationship has not been further elucidated. Beyond specific inherited syndromes, an association between HB and congenital abnormalities has been identified [13,14]; however, since not all congenital abnormalities were specified, many may have been associated with underlying syndromes.

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■ Environmental risk

Multiple environmental risks have been previously investigated. There are several studies showing possible associations between parental tobacco smoking and HB risk [15–17]; however, associations were not identified in other studies [18,19]. Despite these mixed findings, the International Agency for Research on Cancer published a policy statement in 2009 declaring HB a tobacco-related malignancy [20]. Most recently, in a case–control study from the Children’s Oncology Group, no relationship was identified between maternal smoking and HB risk, and a marginal association was observed between paternal smoking in the year prior to pregnancy (odds ratio: 1.4; 95% CI: 1.0–2.0) and during pregnancy (odds ratio: 1.4; 95% CI: 0.9–2.0) and HB risk [21]. Parental occupational exposures, including maternal exposures to metals, petroleum products and paint or pigments, and paternal metal exposures, have also been implicated in HB risk [18]. To date, these findings have not been replicated.

Reproductive history and perinatal exposures have been examined in multiple studies with mixed findings. Maternal age has not been shown to be associated with HB risk [13,17,19,22]. Polyhydramnios and severe pre-eclampsia/eclampsia were identified as risks in one study [14], but have

not been well assessed elsewhere. Increased maternal prepregnancy BMI was identified as a risk in one study and was not associated in another [17,23]. Similarly, use of infertility treatments was initially identified as a potential risk factor [17], but in a more extensive analysis, no association was identified with any infertility treatment or assisted reproductive technology use [24].

■ Neonatal risk

The strongest association with HB identified, to date, has been that of LBW, with increasingly strong associations noted with decreasing birth weight (BW) [13,14,25,26]. This association was first reported in 1996 [27], and has been consistent across geographic locations including: the USA [13,17,22,26], UK [14], Japan [25,28], China [29] and the Nordic countries [19]. Interestingly, recent increased survival rates among LBW and very LBW (<1500 g) infants temporally coincide with the increased incidence of HB [30]. It has also been reported that HB among very LBW children is more likely to be of more advanced tumor stage [31], although sample size was small and findings have not been replicated.

Multiple environmental exposures within the neonatal intensive care unit (NICU) have potential hazardous health impacts [32]. Given the inverse association between BW and HB risk, the association with neonatal treatment duration and intensity has been vigorously investigated. Japanese infants with BW of <750 g with longer exposure to mechanical ventilation and inhaled oxygen, and longer duration of hospitalization had increased risk of HB [33]. Another Japanese case–control study of HB cases with BW of <1000 g, identified furosemide treatment and duration of oxygen therapy as risk factors [34]. Among very LBW Japanese infants who subsequently developed HB, those with more advanced stage tumors were more likely to have been exposed to inhaled oxygen therapy, assisted ventilation, furosemide and phenobarbital during NICU admission [35]. An additional hypothesized NICU exposure has been plasticizers, such as di-(2-ethylhexyl)phthalate, which is used in many medical devices, and is a known hepatocarcinogen in rodents [36]; this has yet to be formally tested. Within the largest case series of LBW HB cases compiled to date, specific neonatal exposures (e.g., respiratory support, total parenteral nutrition, antibiotics, transfusion, phototherapy and diagnostic imaging) could not be confirmed to be associated with HB risk, owing to the high

level of correlation between BW and intensity of NICU therapies [TURCOTTE LM, UNPUBLISHED DATA]. Interestingly, when the cohort was compared with other series of neonates [37,38], it appeared that the HB cases had been exposed to more diagnostic radiographs than infants with similar BWs and NICU lengths of stay.

Future perspective

Much progress has been made in gaining greater understanding of HB etiology; however, given the minimal yield of environmental exposure research, much remains to be discovered. Knowledge regarding the significance or prognostic implications of the above findings is limited and investment into further investigation of the underlying genetics of HB is warranted. Based on the strong association of HB with LBW, it is feasible that the two may share a common genetic etiology. Genome-wide association studies in rare childhood-onset tumors have successfully identified associated genetic variants, despite small sample sizes [1], lending support to future genome-wide association studies of HB. Not only could these investigations shed

further light on the previously reported LBW association with HB, but the data may be useful to neonatologists in better understanding causes and consequences of LBW. In addition, using the same data, more information could be obtained to enhance understanding of pharmacogenetics and toxicogenetics of HB therapy, and of late effects and health outcomes in HB survivors. The time is ripe to move the HB research agenda beyond simple associations and to move toward understanding the genetic underpinnings of this challenging childhood malignancy. These potential discoveries could open the door to improved therapeutic options and enhanced survivorship.

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References

- Raynor LA, Pankratz N, Spector LG. An analysis of measures of effect size by age of onset in cancer genome wide association studies. *Genes Chromosome Cancer* 52, 855–859 (2013).
- Ross JA, Gurney JG. Hepatoblastoma incidence in the United States from 1973 to 1992. *Med. Pediatr. Oncol.* 30, 141–142 (1998).
- Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992–2004). *Cancer* 112, 416–432 (2008).
- Darbari A, Sabin KM, Shapiro CN, Schwarz KB. Epidemiology of primary hepatic malignancies in U.S. children. *Hepatology* 38, 560–566 (2003).
- Tomlinson GE, Kappler R. Genetics and epigenetics of hepatoblastoma. *Pediatr. Blood Cancer* 59, 785–792 (2012).
- DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from the Beckwith–Wiedemann Syndrome Registry. *J. Pediatr.* 132, 398–400 (1998).
- Giardiello FM, Offerhaus JA, Krush AJ *et al.* Risk of hepatoblastoma in familial adenomatous polyposis. *J. Pediatr.* 119, 766–768 (1991).
- Maruyama K, Ikeda H, Koizumi T. Hepatoblastoma associated with trisomy 18 syndrome: a case report and a review of the literature. *Pediatr. Int.* 43, 302–305 (2001).
- Weksberg R, Nishikawa J, Caluseriu O *et al.* Tumor development in the Beckwith–Wiedemann syndrome is associated with a variety of constitutional molecular 11p15 alterations including imprinting defects of KCNQ1OT1. *Hum. Mol. Genet.* 10, 2989–3000 (2001).
- Giardiello FM, Petersen GM, Brensinger JD *et al.* Hepatoblastoma and APC gene mutation in familial adenomatous polyposis. *Gut* 39, 867–869 (1996).
- Mamluk V, Nichols M, Lockhart L, Mamluk R. Trisomy 18 and hepatoblastoma. *Am. J. Med. Genet.* 33, 125–126 (1989).
- Bove KE, Soukup S, Ballard ET, Ryckman F. Hepatoblastoma in a child with trisomy 18: cytogenetics, liver anomalies, and literature review. *Pediatr. Pathol. Lab. Med.* 16, 253–262 (1996).
- Spector LG, Johnson KJ, Soler JT, Puumala SE. Perinatal risk factors for hepatoblastoma. *Br. J. Cancer* 98, 1570–1573 (2008).
- Ansell P, Mitchell CD, Roman E, Simpson J, Birch JM, Eden TO. Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS. *Eur. J. Cancer* 41, 741–748 (2005).
- Pang D, McNally R, Birch JM. Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. *Br. J. Cancer* 88, 373–381 (2003).
- Sorohan T, Lancashire RJ. Parental cigarette smoking and childhood risks of hepatoblastoma: OSCC data. *Br. J. Cancer* 90, 1016–1018 (2004).
- McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Maternal and infant birth characteristics and hepatoblastoma. *Am. J. Epidemiol.* 163, 818–828 (2006).
- Buckley JD, Sather H, Ruccione K *et al.* A case–control study of risk factors for hepatoblastoma. A report from the Childrens Cancer Study Group. *Cancer* 64, 1169–1176 (1989).
- de Fine Licht S, Schmidt LS, Rod NH *et al.* Hepatoblastoma in the Nordic countries. *Int. J. Cancer* 131, E555–E561 (2012).
- Secretan B, Straif K, Baan R *et al.* A review of human carcinogens – part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol.* 10, 1033–1034 (2009).
- Johnson KJ, Williams KS, Ross JA *et al.* Parental tobacco and alcohol use and risk of hepatoblastoma in offspring: a report from the Children's Oncology Group. *Cancer Epidemiol. Biomarkers Prev.* 22(10), 1837–1843 (2013).

- 22 Reynolds P, Urayama KY, Von Behren J, Feusner J. Birth characteristics and hepatoblastoma risk in young children. *Cancer* 100, 1070–1076 (2004).
- 23 Musselman JR, Georgieff MK, Ross JA *et al.* Maternal pregnancy events and exposures and risk of hepatoblastoma: a Children's Oncology Group (COG) Study. *Cancer Epidemiol.* 37, 318–320 (2013).
- 24 Puumala SE, Ross JA, Feusner JH *et al.* Parental infertility, infertility treatment and hepatoblastoma: a report from the Children's Oncology Group. *Human Reprod.* 27, 1649–1656 (2012).
- 25 Tanimura M, Matsui I, Abe J *et al.* Increased risk of hepatoblastoma among immature children with a lower birth weight. *Cancer Res.* 58, 3032–3035 (1998).
- 26 Spector LG, Puumala SE, Carozza SE *et al.* Cancer risk among children with very low birth weights. *Pediatrics* 124, 96–104 (2009).
- 27 Riley HK, Freyer DR. Frequent occurrence of prematurity among children with hepatoblastoma: a preliminary study. *J. Pediatr. Hematol. Oncol.* 18, 446 (1996).
- 28 Ikeda H, Matsuyama S, Tanimura M. Association between hepatoblastoma and very low birth weight: a trend or a chance? *J. Pediatr.* 130, 557–560 (1997).
- 29 Pu CL, Guo CB, Jin XQ *et al.* Retrospective analysis of maternal and infant birth features of hepatoblastoma patients. *Zhonghua Gan Zang Bing Za Zhi* 17, 459–461 (2009).
- 30 Spector LG, Feusner JH, Ross JA. Hepatoblastoma and low birth weight. *Pediatr. Blood Cancer* 43, 706 (2004).
- 31 Ikeda H, Hachitanda Y, Tanimura M, Maruyama K, Koizumi T, Tsuchida Y. Development of unfavorable hepatoblastoma in children of very low birth weight. *Cancer* 82, 1789–1796 (1998).
- 32 Lai TT, Bearer CF. Iatrogenic environmental hazards in the neonatal intensive care unit. *Clin. Perinatol.* 35, 163–181 (2008).
- 33 Oue T, Kubota A, Okuyama H *et al.* Hepatoblastoma in children of extremely low birth weight: a report from a single perinatal center. *J. Pediatr. Surg.* 38, 134–137 (2003).
- 34 Maruyama K, Ikeda H, Koizumi T *et al.* Case-control study of perinatal factors and hepatoblastoma in children with an extremely low birthweight. *Pediatr. Int.* 42, 492–498 (2000).
- 35 Maruyama K, Ikeda H, Koizumi T, Tsuchida Y. Prenatal and postnatal histories of very low birth weight infants who developed hepatoblastoma. *Pediatr. Int.* 41, 82–89 (1999).
- 36 Latini G, Gallo F, De Felice C. Birth characteristics and hepatoblastoma risk in young children. *Cancer* 101, 210 (2004).
- 37 Sutton PM, Arthur RJ, Taylor C, Stringer MD. Ionising radiation from diagnostic x rays in very low birthweight babies. *Arch. Dis. Child. Fetal Neonatal Ed.* 78, F227–F229 (1998).
- 38 Puch-Kapst K, Juran R, Phys D, Stoeber B, Wauer RR. Radiation exposure in 212 very low and extremely low birth weight infants. *Pediatrics* 124, 1556–1564 (2009).

■ Website

- 101 Howlader N, Noone AM, Krapcho M *et al.* SEER cancer statistics review, 1975–2010. National Cancer Institute (2013). http://seer.cancer.gov/csr/1975_2010/ (Accessed 20 August 2013)