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Congenital Abnormalities and Hepatoblastoma: A Report from the Children's Oncology Group (COG) and the Utah Population Database (UPDB)

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Abstract

Beckwith-Wiedemann Syndrome (BWS) and Familial Adenomatous Polyposis (FAP) are known to predispose to hepatoblastoma (HB). A case control study was conducted through the Children's Oncology Group (COG) to study the association of HB with isolated congenital abnormalities. Cases (N = 383) were diagnosed between 2000 and 2008. Controls (N = 387) were recruited from state birth registries, frequency matched for sex, region, year of birth, and birth weight. Data on congenital abnormalities among subjects and covariates were obtained by maternal telephone interview. Odds ratios (OR) and 95% confidence intervals (CI) describing the association between congenital abnormalities with HB, adjusted for sex, birth weight, maternal age and maternal education, were calculated using unconditional logistic regression. There was a significant association of HB with kidney, bladder, or sex organ abnormalities (OR = 4.75; 95% CI: 1.74–13) which appeared to be specific to kidney/bladder defects (OR = 4.3; 95% CI: 1.2–15.3) but not

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those of sex organs (OR = 1.24; 95% CI: 0.37–4.1). Elevated but non-significant ORs were found for spina bifida or other spinal defects (OR = 2.12; 95% CI: 0.39–11.7), large or multiple birthmarks (OR = 1.33; 95% CI: 0.81–2.21). The results were validated through the Utah Population Database (UPDB), a statewide population-based registry linking birth certificates, medical records, and cancer diagnoses. In the UPDB, there were 29 cases and 290 population controls matched 10:1 on sex and birth year. Consistent with the COG findings, kidney/bladder defects were associated with hepatoblastoma. These results confirm the association of HB with kidney/bladder abnormalities.

Keywords

Hepatoblastoma; Beckwith-Wiedemann syndrome; Familial Adenomatous Polyposis; Kidney abnormalities; case-control study; congenital abnormality; congenital anomaly

INTRODUCTION

Hepatoblastoma has been reported in association with a wide variety of congenital abnormalities [Narod et al., 1997; Ansell et al., 2005]. This association is firmly established in two conditions: Beckwith-Wiedemann syndrome (BWS) and Familial Adenomatous Polyposis (FAP) [Hirschman et al., 2005; DeBaun and Tucker, 1998]. In addition, multiple case reports published recently suggests an increased risk of hepatoblastoma in patients born with Trisomy 18 (Pereira et al., 2012). Individual case reports also have been published on hepatoblastoma occurring in patients with Goldenhar syndrome [Corona-Rivera et al., 2006], Noonan syndrome [Yoshida et al., 2008], Trisomy 13 [Shah et al., 2013], Fragile X syndrome [Wirojawan et al., 2008], Sotos syndrome [Kato et al., 2009], Prader-Willi syndrome [Hashizume et al., 1991], Prune belly syndrome [Becknell et al., 2011], Aicardi syndrome [Tanaka et al., 1985], Neurofibromatosis Type 1 [Uçar et al., 2007], and other conditions [Al-Rahawan et al., 2007]. Many of these conditions are extremely rare and it is difficult to accurately estimate the increased hepatoblastoma risk in these patients. Even though the frequency of congenital anomalies has been shown to be much higher in children with hepatoblastoma, no individual congenital abnormality has been definitively shown to be significantly associated with hepatoblastoma in previous studies [Narod et al., 1997; Ansell et al., 2005]. Some reports have suggested an association with hypoplastic glomerulocystic kidney disease and hepatoblastoma [Greer et al., 1998; Abdul-Rahman et al., 2009; Chan et al., 2014].

We examined maternally-reported congenital anomalies in a Children's Oncology Group (COG) case-control study, one of the largest etiologic investigations of hepatoblastoma to date, and validated the results in an independent analysis of cases in the Utah Population Database (UPDB), a statewide population-based registry that is record-linked to the Utah Cancer Registry (UCR), Utah birth certificate data, medical records, and extensive genealogy records.

METHODS

COG Discovery Cohort

We previously have described in detail the methods used in the COG case control study [Musselman et al., 2013; Puumala et al., 2012]. Hepatoblastoma cases were diagnosed at a COG institution between 2000 and 2008. All cases had to be born in the United States and have English- or Spanish-speaking birth mother. Controls were identified from the birth registries from 32 states [Spector et al., 2007] and matched to cases for the following characteristics: birth weight (<1500g, 1500–2500g, and >2500g), gender, birth year and region. A standardized computer assisted telephone interview was administered to the birth mothers and the information was collected on perinatal exposures/events, pregnancy history, family history and birth defects. Several questions specific for congenital anomalies were asked including questions about a diagnosis of BWS, FAP, cleft lip or palate, spina bifida or other spinal defects, large or multiple birth marks, chromosomal abnormalities, microcephaly, rib abnormalities and presence of kidney, bladder or sex organ abnormalities. Any birthmark greater than the size of a quarter was considered large. Six or more birthmarks, each larger than the size of a dime, was defined as multiple birthmarks. The timing of the diagnosis of a birth defect in relation to the diagnosis of hepatoblastoma was not collected.

Unconditional logistic regression was used to examine the association between hepatoblastoma and congenital abnormalities. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using SAS 9 (SAS Institute, Cary, NC, USA). Univariate Fisher's exact test was used to assess the association between congenital anomalies and hepatoblastoma when cell-size was <5. Informed consent was obtained from all participating families. The institutional review board approval was obtained in all participating institutions and from the health departments of states providing birth registry data.

UPDB Validation Cohort

The UPDB is a dynamic resource located at the University of Utah and consists of computerized data records for nearly seven million individuals. It is the only database of its kind in the United States and one of a few in the world; most families living in Utah are represented in the UPDB. The UPDB includes statewide vital records including births that are linked concurrently to individuals in existing multigenerational pedigrees, or used to create new pedigrees. Statewide cancer records from the UCR, a Surveillance Epidemiology and End Results (SEER) registry are record-linked to the UPDB. Approvals were received from the University of Utah's Institutional Review Board (IRB) and Resource for Genetic Epidemiologic Research (the body that reviews potential projects that use the UPDB) to conduct this study. As this non-contact, retrospective-cohort study posed minimal risk to individuals, a waiver of informed consent was obtained.

Hepatoblastoma cases (ICD-O-3 histology 8970 in UCR) were diagnosed in Utah and link to a Utah birth certificate recorded between 1978 and 2010. In 1978, congenital anomalies became electronically available fields in UPDB, in addition to birth weight and maternal age and education level which were available previously. Controls were selected randomly from

the Utah population in UPDB and matched 10:1 to cases for gender and birth year. Congenital anomalies for cases and controls were obtained from Utah birth records in UPDB as the equivalent ICD-9 code corresponding to congenital anomaly text or indicator fields. To supplement data from birth certificates, statewide medical records linked to UPDB were queried for cases and controls to capture diagnoses of congenital anomalies (ICD-9 codes 740–759) diagnosed within 24 months of birth. Diagnosis of suspected BWS was determined for patients with both a diagnosis of ICD9-759.89 (other specified congenital anomalies) and macroglossia (ICD-9 750.15), a feature commonly associated with BWS. An ICD-9 diagnosis of 757.32 (vascular hamartomas) provided an indication of ‘large or multiple birth marks.’ Similarly, other congenital anomalies of interest were characterized from ICD-9 codes 740-759 as follows: cleft lip or palate (749); spina bifida (741); Trisomy 18 (758.2); Down syndrome (758.0); rib abnormalities (756.2–756.7); small head/microcephaly (742.1); hypospadias (752.6); kidney/bladder deformities (753); sex organ anomalies (752, excluding 752.6).

Conditional logistic regression was used to examine the association between hepatoblastoma and congenital abnormalities adjusted for birth weight (category), maternal age, maternal education (category). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using SAS 9.1.3 (SAS Institute, Cary, NC, USA). Fisher’s exact test was used to assess the association between congenital anomalies and hepatoblastoma in cases and controls, as cell sizes were small.

RESULTS

COG Discovery Cohort

Mothers of 383 cases and 387 controls completed the study interview between 2005 and 2010. Twelve cases were reported to have BWS and 4 to have FAP, while no controls had either condition; further analyses excluded abnormalities among children with these syndromes to better examine isolated defects. Demographic characteristics of cases and controls and their birth mothers are given in Table I. Cases were more likely to be male and fifteen percent of cases had very low birth weight.

Twenty percent of cases and 10 percent of controls had at least one of the evaluated congenital abnormalities (Table II). There was a significant association of HB with kidney, bladder, or sex organ abnormalities (OR = 4.75; 95% CI: 1.74–13). Five percent of cases (N = 18) and 1.6 percent of controls (N = 6) reported an abnormality of kidney, bladder or sex organ. On further analysis, this association appeared to be specific to kidney/bladder defects (OR = 4.3; 95% CI: 1.2–15.3) but not those of sex organs (OR = 1.24; 95% CI: 0.37–4.1). Kidney defects reported in cases included polycystic kidney disease (N = 1), single kidney (N = 1), hypoplastic kidneys (N = 1), enlarged kidney (N = 2), ureteral abnormality (N=3), unspecified bladder abnormality (N = 1) and kidney failure (N = 3). Elevated but non-significant ORs were found for spina bifida or other spinal defects (OR = 2.12; 95% CI: 0.39–11.7), large or multiple birthmarks (OR = 1.33; 95% CI: 0.81–2.21). One case each had Trisomy 13, Rubinstein Taybi Syndrome, and Simpson-Golabi-Behmel Syndrome while none of the controls had these conditions. No significant associations of cleft lip or palate, Down syndrome or other genetic conditions, microcephaly, or rib abnormalities were found,

although less than four subjects were reported to have each of these defects, precluding precise estimation of ORs.

UPDB Validation Cohort

Thirty three cases of hepatoblastoma and 330 controls born between 1978 and 2010 were identified from the Utah Population Database. Of these, four cases had a probable diagnosis of BWS, and were excluded from further analysis leaving 29 cases and 290 controls in the analysis (Table III). There was a significant association of hepatoblastoma with combined kidney/ bladder defects or sex organ abnormalities (OR = 12.0; 95% CI: 1.61–89.6; *P*-Fisher's=0.006). Ten percent of cases (N=3) and 0.7% of controls (N=2) had an abnormality of kidney, bladder or sex organ. In addition to kidney/bladder defects (OR 99.0; *P*-Fisher's=0.008), sex organ anomalies (OR=25.7; *P*-Fisher's=0.02) were associated with hepatoblastoma. Although not surveyed in the COG study, we observed increased risk of congenital heart and pulmonary anomalies in hepatoblastoma cases (OR=7.4; 95% CI: 0.9–62.7; *P*-Fisher's=0.04).

To further investigate the association between hepatoblastoma and GU anomalies, the risk for hepatoblastoma among individuals with GU anomalies was evaluated. There were 30,386 individuals with GU anomalies identified in UPDB (diagnosed 1978-present). Statewide controls were matched to GU cases at a ratio of 10:1. Cases with GU anomalies were found to have an increased risk of developing hepatoblastoma (OR=7.3; 95% CI: 1.2–43.8; *P*-Fisher's=0.03). First and second degree relatives of cases did not exhibit a significantly increased risk (OR=3.9; 95% CI: 0.4–35.5; *P*-Fisher's=0.22).

DISCUSSION

Ours is the largest case control study of congenital anomalies and hepatoblastoma and appears to be the first to describe an association with genitourinary anomalies; an independent population-based dataset confirmed the association. The prior literature consists of only two case-control studies. In a large population based case-control study of 165 cases, children with hepatoblastoma were more likely to have a congenital anomaly when compared to those with leukemia and lymphoma [Narod et al., 1997]. Of those with hepatoblastoma, 6.4% had congenital anomalies, but no specific or recurring anomaly was identified as significant. A subsequent smaller case control study with 22 patients with hepatoblastoma reported 50% incidence of congenital anomalies, including one patient with bilateral hydronephrosis and another patient with bilateral ureteric reflux and undescended testicles [Ansell et al., 2005]. In our study, 20% of cases had a congenital anomaly. The difference in the reported incidence of congenital anomalies between published studies may be the result of different definitions of congenital anomalies and the method of ascertainment which ranged from parental self-report to data abstraction from patient/ population registries. None of the previous case control studies reported an association of hepatoblastoma with a specific congenital anomaly including genitourinary anomalies.

We excluded known genetic causes (BWS and FAP) in the final analysis to increase the chances of finding new novel associations. Although only one case had Trisomy 13, at least 12 cases of hepatoblastoma in children with Trisomy 13 have been published to date

[Pereira et al., 2012; Tan et al., 2013]. The association of Trisomy 18 and hepatoblastoma was recently reported [Shah et al., 2013]. An additional patient described in our report further strengthens this association. Given the rarity of these two trisomy syndromes [Rasmussen et al., 2003], there is likely an etiological association with hepatoblastoma rather than a coincidence. Due to high mortality during infancy, some of these children may die before the developing clinically obvious hepatoblastoma.

Children with structural, non-chromosomal birth defects, including renal defects, also have an increased risk for developing childhood cancer [Botto et al., 2013; Bjørge et al., 2008]. Several recent reports have suggested an association between cystic disease of the kidney and hepatoblastoma [Greer et al., 1998; Abdul-Rahman et al., 2009; Chan et al., 2014]. The association between kidney/bladder defects and hepatoblastoma was significant in our study and in the Utah validation cohort. Since the congenital anomalies in the COG patients were maternally-reported, the precise nature of the kidney defect could not be ascertained in many patients. Some of the mothers reported enlarged kidney or kidney failure in their children with hepatoblastoma. These patients may have had underlying polycystic or glomerulocystic disease of the kidney. This association is not surprising as liver and kidney problems also occur together in other situations. Overgrowth syndromes such as BWS predisposes to both liver and kidney malignancy. Liver involvement is the most frequent extra renal manifestation in autosomal recessive polycystic kidney disease (PKD) [Chauveau et al., 2000]. Though cysts in the liver develop during adulthood, congenital hepatic fibrosis is very common in PKD [Gunay-Aygun et al., 2013]. Mutations in *PKHD1* are responsible for liver and kidney manifestations. Whether cystic kidney disease seen in patients with hepatoblastoma represents a distinct entity with specific underlying genetic defect or falls under the spectrum of manifestations of polycystic kidney disease requires further investigation.

Although the Utah replication set contained only 29 non-BWS cases with congenital anomalies, it represents a population rather than clinic-based confirmation that did not rely on self- or family-reported congenital anomalies. In addition, 10:1 matched controls were analyzed in order to increase the power for detection. The data was obtained from statewide birth and medical records linked to comprehensive cancer diagnoses in the UPDB. Although odds ratio estimates were imprecise, a statistically significant association of hepatoblastoma with kidney/bladder defects and sex organ anomalies was observed. The findings were further validated by confirming that cases presenting with GU anomalies also exhibit an increased risk for hepatoblastoma.

Even though this is the largest case control study of risk factors of hepatoblastoma, the sample size may not be large enough to establish associations with very infrequent abnormalities. The potential for recall bias is likely low for congenital anomalies and not relevant for population-based registries like the UPDB, but the detection rates may differ between cases and controls. It is possible that patients with hepatoblastoma in our study had increased contact with healthcare professionals and therefore had more imaging studies that resulted in higher rates of detection of congenital anomalies when compared to controls. Despite this, the recurrent finding of an association between hepatoblastoma and congenital kidney and sex organ anomalies in both the COG and UPDB cohorts suggests a true finding.

However, the power of this confirmation is hampered by the very low incidence of hepatoblastoma, and more validation studies are needed.

The ultimate goal of these types of investigations is to identify factors that may predict those children at greatest risk for hepatoblastoma in order to provide opportunities for screening and early detection. GU anomalies may be diagnosed at birth, prior to cancer development. This analysis indicates that while children presenting with GU anomalies have an increased hepatoblastoma risk, the absolute risk is still small. The magnitude of risk does not reach the level associated with FAP and Beckwith-Wiedemann syndrome, conditions for which hepatoblastoma screening protocols have been developed. However, based on the growing body of research supporting an association between congenital anomalies and malignancy, all children presenting with congenital anomalies, particularly those with GU anomalies, should have a careful evaluation for additional features which may indicate a cancer predisposing syndrome. Genetic sequencing of germline and tumor DNA from hepatoblastoma patients with kidney defects is currently underway and may help to elucidate the genetic basis of this association and possibly even define new genetic syndromes. This may lead to new early screening programs for hepatoblastoma in high risk patients that can identify early stage tumors and improve morbidity and mortality associated with this specific pediatric cancer.

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Table I

Demographic characteristics of cases and controls

Demographic	Controls (%) N=387	Cases (%) N=367	Crude OR	95% CI
Sex				
Male	225 (58)	219 (60)	Ref	
Female	162 (42)	148 (40)	0.94	0.70, 1.26
Birth weight (grams)				
<1500	65 (17)	55 (15)	3.34	1.82, 6.14
1500–2500	79 (20)	20 (5)	Ref	
>2500	243 (63)	292 (80)	4.75	2.82, 7.98
Maternal education				
<8	6 (1.6)	18 (5)	3.50	1.34, 9.13
8–11	11 (3)	26 (7)	2.76	1.30, 5.84
HS	68 (18)	63 (17)	1.08	0.70, 1.66
Post-HS	30 (8)	18 (5)	0.70	0.37, 1.33
Some college	77 (20)	84 (23)	1.27	0.85, 1.90
College	126 (33)	108 (30)	Ref	
Adv. degree	65 (17)	47 (13)	0.84	0.54, 1.33
Missing	4	3		
Maternal race				
White	284 (75)	250 (69)	Ref	
Black	33 (9)	16 (4)	0.55	0.30, 1.03
Hispanic	34 (9)	69 (19)	2.31	1.48, 3.60
Other	30 (8)	28 (8)	1.06	0.62, 1.82
Missing	6	4		
Maternal age				
<20	15 (4)	26 (7)	2.23	1.12, 4.44
20–24	66 (17)	57 (16)	1.11	0.71, 1.73
25–29	122 (32)	95 (26)	Ref	
30–34	113 (29)	122 (33)	1.39	0.96, 2.01
35+	68 (18)	67 (18)	1.27	0.82, 1.95
Missing	3	0		

Table II

Association between hepatoblastoma and congenital anomalies

Variable of Interest	Controls (%) N=387	Cases (%) N=367	OR (CI)	Fisher's p-value
Cleft lip or palate	1 (0.3)	1 (0.3)	1.05 (0.07, 16.9)	1.00
Spina bifida or other spinal defect	2 (0.5)	4 (1.1)	2.12 (0.39, 11.7)	0.44
Large/multiple birthmarks	30 (7.8)	37 (10.1)	1.33 (0.81, 2.21)	0.31
Trisomy 18	0 (0.0)	1 (0.3)	-	0.49
Other genetic conditions	1 (0.3)	2 (0.5)	2.11 (0.19, 23.4)	0.61
Down syndrome	1 (0.3)	0 (0.0)	-	1.00
Rib abnormalities	0 (0.0)	1 (0.3)	-	0.49
Small head/microcephaly	0 (0.0)	3 (0.8)	-	0.11
Kidney, bladder, sex organ abnormality	6 (1.6)	18 (4.9)	4.75 (1.74, 13.0)	0.01
Hypospadias *	2 (0.5)	4 (1.1)	2.1 (0.38, 11.4)	0.44
Any kidney/bladder *	3 (0.8)	12 (3.3)	4.3 (1.2, 15.3)	0.02
Sex organ *	5 (1.3)	6 (1.6)	1.24 (0.37, 4.1)	0.77

* Controlled for sex (Ref=Male)

Table III

Association between hepatoblastoma and congenital anomalies in Utah Population Database

Variable of Interest	Controls (%) N=290	Cases (%) N=29	OR (CI) *	Fisher's p-value
Cleft lip or palate	0 (0.0)%	0 (0.0)%	--	--
Spina bifida	0 (0.0)%	0 (0.0)%	--	--
Large/multiple birthmarks	1 (0.3)%	0 (0.0)%	--	1.0
Trisomy 18	0 (0.0)%	0 (0.0)%	--	--
Other genetic conditions	0 (0.0)%	0 (0.0)%	--	--
Down syndrome	1 (0.3)%	0 (0.0)%	--	1.0
Rib abnormalities	1 (0.3)%	1 (3.4)%	4.3 (0.23, 80.0)	0.17
Small head/microcephaly	0 (0.0)%	0 (0.0)%	--	--
Kidney, bladder, sex organ abnormalities	2 (0.7)%	3 (10.3)%	12.0 (1.61, 89.6)	0.006
Hypospadias	1 (0.3)%	0 (0.0)%	<0.001 (n/a)	1.0
Any kidney/bladder	0 (0.0)%	2 (6.9)%	>99 (n/a)	0.008
Sex organ anomalies	1 (0.3)%	1 (3.4)%	25.7 (1.63, >99)	0.02
Heart or pulmonary anomalies	2 (0.7)%	2 (6.9)%	7.4 (0.87, 62.7)	0.04

* Controls were matched 10:1 to cases on sex and birth year; model covariates include birth weight, maternal age, and maternal education.