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Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS

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Abstract

Within the context of a national population-based case-control study – the United Kingdom Childhood Cancer Study (UKCCS) – we aimed to explore relationships between perinatal and maternal factors and childhood hepatic tumours, for participants with data available from medical records. 26/28 children with hepatic tumours (22/24 hepatoblastomas, 4/4 hepatocellular carcinomas (HCC)) and 4753 age- and sex-matched controls were included. Polyhydramnios was associated with 0.9% of control pregnancies and 13.6% of case pregnancies (Odds Ratio (OR) = 28.64, 95% Confidence Interval (CI) = 6.94–118.21, $P < 0.0001$); eclampsia or severe pre-eclampsia complicated the pregnancies of 16.7% of mothers whose children developed hepatoblastoma compared with 0.5% of control pregnancies (OR = 52.50, 95% CI = 10.75–257.05, $P < 0.0001$). Three children with hepatoblastoma weighed <1500 g at birth, two of whom weighed <1000 g (OR for birthweight <1500 g = 69.00, 95% CI = 11.98–397.17, $P < 0.0001$). Of children with hepatoblastoma, 50% (11/22) had records of congenital anomalies, as did two of their mothers. Three mothers of children with hepatoblastoma had diagnoses of cancer – two of papillary carcinoma of the thyroid and one of acute lymphoblastic leukaemia (ALL). Paediatricians and others should be alert to the possibility of familial or genetic syndromes in children with hepatoblastomas. Potential links between maternal pre-eclampsia, low birthweight and subsequent malignancy merit further investigation. Hepatoblastoma is an extremely rare childhood tumour, but understanding the mechanism(s) underlying severe pre-eclampsia and eclampsia may also shed light on factors that contribute to the development of hepatoblastoma.

Keywords: Hepatoblastoma; Low birthweight; Pre-eclampsia; Polyhydramnios; Congenital anomalies

1. Introduction

Malignant tumours of the liver are extremely rare in children and are most usually hepatoblastomas. Diagnosis is most frequently made in children less than 3 years of age [1–5]. Hepatocellular carcinoma (HCC) tends to occur in older children and is commonly associated with hepatitis B and C infections or with metabolic and other disorders which damage the liver and lead to cirrhosis [2,6,7].

Recent reports from Japan [8–10] and the United States of America (USA) [3,4,11,12] suggest that the

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incidence of hepatoblastoma may be increasing, an increase which appears to be associated with the improved survival of very low birthweight (VLBW; <1500 g) and extremely low birthweight (ELBW; <1000 g) babies. It is not clear why VLBW should be associated with hepatoblastoma, suggestions being either that some facet(s) of advanced neonatal intensive care is a factor [9–11,13–15] or that affected children did not previously survive [16].

An association between embryonal tumours and congenital anomalies is, however, well established. Children with overgrowth syndromes such as Beckwith-Wiedemann (BWS) and Simpson-Gobali-Behmel, and with congenital anomalies that are features of such syndromes, are known to be at increased risk [2,17–19]. The incidence of hepatoblastoma is also greatly increased in familial adenomatous polyposis coli (FAP), where affected individuals are known to carry germline mutations in the *APC* gene [20–24]. More recently, the genetic basis of some abnormalities in BWS, including tumour development, have been proposed [25–29].

This report describes the characteristics of children with hepatic tumours enrolled in the United Kingdom Childhood Cancer Study (UKCCS), based on an analysis of obstetric, neonatal and general practitioner (GP, primary care) records of children and their mothers. Data from the Scottish component of the UKCCS are not included as obstetric data for Scotland have been published elsewhere [30].

2. Patients and methods

The UKCCS is a national population-based case-control study, full details of which are described elsewhere [31,32]. Briefly, children aged 0–14 years diagnosed with cancer between 1992 and 1996 were eligible for inclusion. Children with non-haematological cancers, including hepatic tumours, were recruited from 1992 to 1994, and children with haematological malignancies were recruited from 1992 to 1996. All solid tumour diagnoses, with the exception of some tumours of the central nervous system, were histologically verified. For each case, two controls matched by sex, month and year of birth, and region of residence at diagnosis were randomly selected from population registers held by the (former) Family Health Service Authorities. At the time of interview, parents were asked for their consent to access their own and their child's medical records, including maternity records.

Information was systematically abstracted from obstetric and neonatal records by specially trained abstractors onto a previously validated, structured form [33]. Given the marked, and continuing, changes in maternal and neonatal care over the years, this form was specially designed to be applicable across hospitals and time periods. For general practitioner (GP, primary care) records, a data abstraction form and data processing methods were especially developed for the UKCCS. All information recorded in children's GP (primary care) records was abstracted. The data include all signs, symptoms and diagnoses recorded for each consultation with the GP from birth until the date of diagnosis (pseudo-diagnosis for controls); referrals to hospital consultants and other specialists up to the date of abstraction; results of investigations; and details of immunisations, drugs and other treatments prescribed. For parents, in addition to a lifetime abstraction of all serious and/or chronic conditions (for example, cancers, autoimmune disease, chronic infections), detailed information for each consultation in the 10 years before the child's birth (plus one year after the birth for mothers) was abstracted.

The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) is the basis for coding symptoms, illnesses and related conditions. In order to utilise the available data fully, and to facilitate accuracy and consistency in coding, we developed a specialist coding scheme to bridge the gap between the terminology used in medical records and ICD-10 classifications, based on a scheme originally designed for a previous study using data from maternity records [33]. The coding scheme alphabetically lists more than 4000 items, together with their appropriate ICD-10 code: this listing is incorporated as a 'pick-list' in the data-entry programs. Additionally, as no comprehensive drug-coding scheme was available, we developed a scheme based on the British National Formulary (BNF Number 24, September 1992 edition).

Analyses were conducted using the statistical software package for epidemiologists STATA (version 8.0) (StataCorp, 2003) and Odds Ratios (ORs), 95% Confidence Intervals (CIs) and two-sided *P*-values were estimated using unconditional logistic regression [34] with adjustment for sex, age at diagnosis, and study region.

3. Results

Overall, data from medical records were abstracted for 26/28 (92.9%) children with hepatic tumours: 24 (85.7%) had data obtained from obstetric and neonatal records, 23 (82.1%) from the child's GP (primary care) records and 21 (75.0%) from the mother's GP records (Table 1). No medical records were traced for two subjects with hepatoblastoma. All available controls, excluding those who were the products of multiple pregnancies (108, 2.2%) or had Down's syndrome (3, <1%), were used as the comparison group for the obstetric analyses (4753 controls) [32].

Table 2 shows the distribution of cases and controls, associated ORs and 95% CIs for complications in the

Table 1
Interviewed cases, numbers (%) and sources of medical records abstracted, and year of birth of cases with records available

	Total *N* (%)
Parents interviewed	28 (100.0)
Medical records abstracted – any	26 (92.9)
Type of records abstracted	
Obstetric & neonatal	24 (85.7)
GP[a] records (child)	23 (82.1)
GP[a] records (mother)	21 (75.0)
Year of birth	
⩽1990	7 (26.9%)
1991–1994	19 (73.1%)

[a] GP = general medical practitioner (primary care).

index pregnancy, for subjects with obstetric data available. Children who were the products of multiple pregnancies have been excluded because of the potentially confounding effects of multiplicity on the obstetric factors investigated. Polyhydramnios was associated with 0.9% of control pregnancies and 13.6% of case pregnancies. Eclampsia or severe pre-eclampsia (ICD-10 codes O14.1 and O15.0-9) complicated the pregnancies of 16.7% of subjects with hepatoblastoma, compared with only 0.5% of control pregnancies. Three children with hepatoblastoma weighed less than 1500 g at birth, two of whom were less than 1000 g. All three were born after 1990. ORs for each of the complications shown in Table 2 were significantly raised ($P < 0.0001$). Fig. 1 illustrates the cumulative frequencies (%) of birthweight for children with hepatic tumours, for hepatoblastoma separately, and for the control group.

We found no other significant differences between pregnancies of case and control mothers – only those characteristics for which significant associations were found are reported.

Birth, pregnancy, and maternal characteristics of the 22 children with hepatoblastoma are shown individually for each child in Table 3, with children listed in order of age at time of tumour diagnosis. Twenty of the children (90.9%) were younger than 5 years of age at the time of diagnosis (age range 6 months–14 years, median age 20 months). The male/female ratio was 2.7 (16 boys, 6 girls). Six of the 22 children (27.3%), all boys, were born prematurely (gestation <37 weeks); and 4 (18.2%), 3 boys and 1 girl, were small for gestational age (below the 25th percentile for gestational age). Two of the 22 children with hepatoblastoma (9.1%) were the products of twin pregnancies, compared with less than 1.3% expected [35]. One of these (case 11) was conceived by *in vitro* fertilisation (IVF). The proportion of children recorded as having congenital anomalies is striking – 50.0% (11/22). One child not recorded as having a congenital anomaly himself (case 09) had a same-sex twin with malrotation of the intestine.

Two mothers had congenital anomalies (cases 09, 13), one of whom had an anomaly that was possibly a feature of a more complex syndrome in her child – cleft palate in the mother associated with velo-cardio-facial syndrome (VCFS) in her child (case 13). Three mothers had diagnoses of cancer – two of papillary carcinoma of the thyroid (cases 02, 18) and one of acute lymphoblastic leukaemia (ALL) (case 03). One mother with papillary carcinoma of the thyroid also had severe pre-eclampsia; her child (case 18) had congenital anomalies (Table 3).

4. Discussion

A variety of congenital defects and other disorders have been reported as associated with the subsequent development of hepatic tumours in childhood. The association between hepatoblastoma and hemihypertrophy is well known [2], as is that with BWS, and with FAP. There is accumulating evidence that very low birthweight (BW <1500 g) may also be associated with the subsequent development of hepatoblastoma, an interesting observation that is counter-intuitive given the known association with overgrowth syndromes. We were unable to investigate whether changes in neonatal

Table 2
Numbers of subjects[a] [%], Odds Ratios (95% Confidence Intervals), distributed by complications in index pregnancy (England and Wales)

		Controls	Cases	
			Hepatoblastoma	All hepatic tumours
		N = 4753	*N* = 18	*N* = 22
Polyhydramnios	All diagnoses	41 [0.9]	2 [11.1]	3 [13.6]
	OR(95% CI)	–	25.72 (4.52–146.20)	28.64 (6.94–118.21)
Pre-eclampsia & eclampsia	Severe[b]	25 [0.5]	3 [16.7]	3 [13.6]
	OR(95% CI)	–	52.50 (10.75–257.05)	35.09 (8.12–151.75)
Baby very low birthweight[c]	All recorded	21 [0.4]	3 [16.7]	3 [13.6]
	OR(95% CI)	–	69.00 (11.98–397.17)	52.53 (10.62–259.79)

[a] Excludes multiple births (2 cases with hepatoblastoma; 108 controls) and children with Down's syndrome (3 controls).
[b] ICD-10 codes O14.1 and O15.0–9.
[c] Birthweight <1500 g.

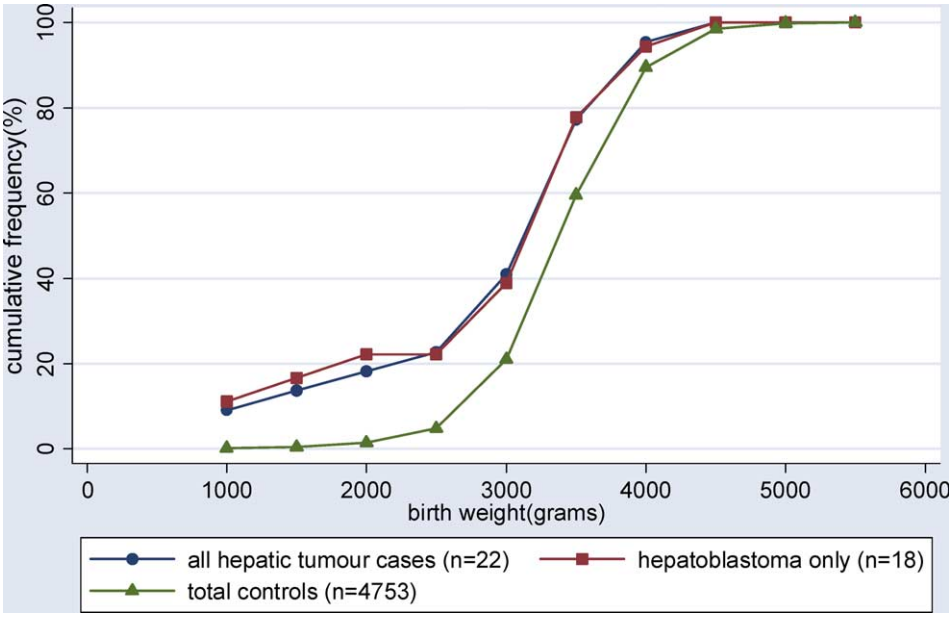

Fig. 1. Cumulative frequencies (%) of birthweight for children with hepatic tumours, for hepatoblastoma separately, and for the control group (excludes subjects without obstetric notes (4) and multiple births (2)).

management over recent years have had any influence on the development of hepatoblastoma. There were no recognised cases of BWS or hemihypertrophy and there was no association between heavier birthweight and hepatoblastoma in our data, although this may be because of our small number of cases. To our knowledge, FAP had not been diagnosed in any of the families.

Additionally, our study identified polyhydramnios and eclampsia/severe pre-eclampsia as being associated with hepatoblastoma. As there were only four cases of HCC, we were unable to investigate any meaningful associations for HCC. In our patients, polyhydramnios was always associated with severe congenital anomalies in the child; and low birthweight was strongly associated with severe pre-eclampsia/eclampsia and with short gestation. Although low birthweight has previously been described in association with hepatoblastoma, severe pre-eclampsia/eclampsia, so far as we are aware, has not. Maruyama and colleagues reported maternal pre-eclampsia in one of 12 extremely low birthweight children with hepatoblastoma and 19/74 birthweight-matched controls (OR = 0.263; CI = 0.032–2.176), but presented no data on the severity of disease [14]. Pre-eclampsia is a highly variable condition, but has been described as impossible to define because its precise cause is unknown [36]. Nonetheless, definitions of pre-eclampsia have changed over time [37] and it may be that other investigators have included gestational hypertension in their definition of pre-eclampsia (ICD-10 code = O13, also described as 'mild pre-eclampsia') and so have failed to find any association. Importantly, our data were collected from medical records, allowing us to identify pregnancies complicated by severe pre-eclampsia or eclampsia (ICD-10 codes = O14.1 and O15.0-9) – these are known to be more likely to result in adverse outcomes for mother and child [37]. All diagnoses were validated against other sources of information, and were systematically reviewed by one of the authors and a senior academic midwife who was unaware of the case-control status. The association between hepatoblastoma and low birthweight, which we and others have noted, may in fact be a consequence of the link between low birthweight and severe pre-eclampsia/eclampsia and it may be the latter that is related to the subsequent development of hepatoblastoma.

Of the seven children whose tumours were detected at less than 12 months of age, only one was born prematurely and only one had a record of congenital anomalies. One explanation for the latter may be that detailed data from children's GP records were only abstracted up to the date of diagnosis (date of abstraction for hospital referrals) – not all congenital anomalies are identified at birth, and for the youngest children there would have been less time for some anomalies (e.g. developmental delay; renal tract anomalies) to become apparent. However, it is also possible that we have a range of associations – hepatoblastomas developing in children with overgrowth syndromes (although no such cases were seen in this series) and congenital anomalies; hepatoblastomas developing secondarily to intrauterine growth retardation and/or severe maternal pre-eclampsia and eclampsia; and some children without evidence of congenital anomalies, but with a maternal history of malignancy. Three of our five heaviest babies were

Table 3
Characteristics of children with hepatoblastomas, pregnancies, and mothers, listed by age of child at time of tumour diagnosis

Child characeristics					Pregnancy	Mother
ID	Sex M/F	BW[a] (g)	Gest[b] (weeks)	Congenital anomalies (ICD-10[c])	Complications [Gest[b] – weeks] (ICD-10[c])	Congenital anomalies and serious chronic conditions (ICD-10[c])
Child's age <12 months at diagnosis						
01	F	3740	40	*Failed to thrive from birth*	–	(*No GP notes*)
02	M	3740	41	*Failed to thrive from birth*	–	Papillary carcinoma of thyroid (C73.X)
03	F	2863	38	–	–	Acute lymphoblastic leukaemia (C91.0)
04	M	1620	33	–	Oligohydramnios [31] (O41.0) Severe pre-eclampsia [32] (O14.1)	–
05	M	3880	38	–	Mild pre-eclampsia [37] (O13.X)	–
06	M	3220	39	Unequal leg lengths (Q74.8)	–	(*No GP notes*)
07	F	3040	38	–	–	–
Child's age 12–23 months at diagnosis						
08	F	3040	39	–	–	–
09	M	3190	39	Twin[d]	–	Cutis laxa (Q82.8)
10	M	3190	38	(*No GP notes*)	–	(*No GP notes*)
11	M	2250	34	Twin[e]	*In vitro* fertilisation	–
12	F	4300	41	Unequal leg lengths (Q74.8)	–	–
13	M	3402	40	Velo-cardio-facial syndrome (Q87.0) Umbilical hernia (K42.9)	Polyhydramnios [28] (O40)	Cleft palate (Q35.9)
14	F	2980	40	–	–	
Child's age 2–4 years at diagnosis						
15	M	0620	26	Cardiomyopathy (I42.4) Developmental delay (F83.X)	Eclampsia [26] (O15.0)	
16	M	0894	27	Absent septum pellucidum (Q04.3)	SROM[f] [26] (O42.1)	–
17	M	3230	39	Bilateral hydronephrosis (Q62.0)	Fetal anomaly on scan [11] (O28.3)	–
18	M	1410	30	Bilateral ureteric reflux (Q62.7) Undescended testes (Q53.2) Coeliac disease (K90.0)	Severe pre-eclampsia [29] (O14.1) Thyroid swelling [0–30]→→	Papillary carcinoma of thyroid (C73.X) *Diagnosis after child's birth*
19	M	2550	34	Congenital heart disease – Ebstein's anomaly (Q22.5) (*no GP notes*)	Irregular fetal heartbeat [29] (O35.8) Polyhydramnios [32] (O40.0) Fetal anomaly on scan [32] (O28.3)	(*No GP notes*)
20	M	3345	40	Talipes (Q66.8) Perthe's disease (M91.1)	(*No obstetric notes*)	–
Child's age ⩾5 years at diagnosis						
21	M	3710	40	Metatarus varus (Q66.2) Femoral anteversion (Q65.8) Right inguinal hernia (K40.9) Microcephaly (Q02)	(*No obstetric notes*)	–
22	M	3260	40	Right inguinal hernia (K40.9)	–	–

M, male; F, female.
[a] BW = birthweight.
[b] Gest = gestation.
[c] International Statistical Classification of Diseases and Related Health Problems 10th revision.
[d] Male twin, BW 2830 g, has congenital malrotation of intestine (Q43.3).
[e] Male twin, 1970 g.
[f] SROM = spontaneous rupture of membranes.

diagnosed at less than 12 months, with the two youngest at diagnosis known to have failed to thrive from birth.

The association between FAP and hepatoblastoma is well known [38]. Thyroid carcinoma occurs at a higher frequency in FAP patients than in the general population with the largest FAP registers reporting an incidence of 1–2% [39]. Although the association between the three conditions has not previously been described, it is possible that the common underlying genetic mechanism in these families is mutation in the *APC* gene – although we found no record of a personal or family history of FAP in the GP records of our patients or their mothers. Truta and colleagues reported that FAP-associated thyroid cancer in their patients was predominantly papillary carcinoma, and occurred in the setting of classic FAP phenotype – germline mutations in the

APC gene were found in 12 out of 13 patients tested [39]. There is, as far as we are aware, only one previous report of hepatoblastoma and ALL in a family – Rafsanjani and Vossough described a two-year-old boy with ALL and his 10-month-old sister with hepatoblastoma [40].

There have been two previous case reports of hepatoblastoma occurring in children conceived by IVF [13,41]. There is also a reported association between IVF and BWS, which appears to be linked specifically with intracytoplasmic sperm injection (ICSI) [42]. Given the well-known predisposition of patients with BWS to develop hepatoblastoma and other embryonal tumours, an association between IVF and hepatoblastoma would be consistent with these two observations. The precise nature of the link between ICSI and BWS remains speculative, but may be related to inappropriate imprinting, possibly of genes in the chromosome region 11p15 [27] as a consequence of the ICSI technique. The association and underlying mechanisms clearly require further investigation.

Many of the congenital anomalies described in our patients, although varied in nature, have been previously reported in association with BWS [43–46]. Unequal leg lengths were seen in two patients, neither of which were recognised at birth. Renal anomalies have previously been described in a patient with hepatoblastoma [2] and we have described two such patients. Developmental delay was diagnosed in one child, in association with extremely low birthweight and cardiomyopathy.

The number of cases included in our study is relatively small, but congenital anomalies were identified in 50% of the children. This is in broad agreement with Mann and colleagues [2] who reported congenital anomalies or possibly related features in 6 of 27 children with hepatoblastomas (5 with congenital anomalies and one with a family history of FAP) registered on the West Midlands Regional Children's Tumour Registry between 1957 and 1986; and with Hartley and colleagues [1] who found congenital anomalies in 6 of 20 children with hepatoblastomas on the Manchester Children's Tumour Registry between 1954 and 1988, and which also included a case associated with FAP. These studies are in marked contrast to the much smaller proportion of congenital anomalies reported by Narod and colleagues (4.4% for all solid tumours; 7.3% for all liver tumours; 6.4% for hepatoblastomas) in 20 304 children with cancer on the British National Registry of Childhood Tumours [47]. This is, however, likely to be an underestimate because comprehensive data on congenital anomalies is not collected systematically for all children on the register.

5. Summary and conclusions

BWS and associated abnormalities are already known to predispose to the development of hepatoblastomas or other tumours. The higher incidence of congenital anomalies reported by us seems in large part due to the collection of details recorded in GP (primary care) records. It is important for paediatricians and others to look for, and record, congenital anomalies in children with hepatoblastoma and to be alert to the possibility of familial or genetic syndromes. Consistent with previous reports, we have also noted the association between low birthweight and hepatoblastoma. In addition, we have noted that low birthweight is associated with severe pre-eclampsia and eclampsia. This finding raises the interesting possibility that the aetiological factor in the subsequent development of hepatoblastoma may, in fact, be maternal pre-eclampsia/eclampsia rather than low birthweight *per se*. The central role of the placenta in the pathogenesis of pre-eclampsia is well known [36]. A secondary component of the condition is maternal systemic illness; and there are also ill-defined links between the two [36]. The potential links between maternal pre-eclampsia, low birthweight and subsequent malignancy is an area that might benefit from further research. Hepatoblastoma is an extremely rare childhood tumour, but understanding the mechanism(s) underlying severe pre-eclampsia and eclampsia may also shed light on factors that contribute to the development of hepatoblastoma.

Conflict of interest statement

None declared.

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