Journal of Pediatric Rehabilitation Medicine: An Interdisciplinary Approach 13 (2020) 185–188
DOI 10.3233/PRM-190662
IOS Press

Case Report

The association of hepatoblastoma, prematurity and cerebral palsy: Case reports

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Abstract.
PURPOSE: Hepatoblastoma is the most common primary liver tumor in children and has a greater incidence in children with a history of prematurity and very low birth weight. To increase awareness of the association between prematurity and hepatoblastoma for health care providers who treat children with Cerebral Palsy (CP), we present two case reports.
METHODS: Two case reports of premature, very low birth weight infants with hepatoblastoma are described and a literature review of hepatoblastoma in the setting of prematurity and cerebral palsy is performed.
RESULTS: Each patient had a history of 26–28 week prematurity, very low birth weight, and CP. Both presented with worsening constipation and abdominal distension that did not respond to oral medications. Appropriate referrals to the ER were made which lead to a diagnosis of hepatoblastoma. Pediatric rehabilitation was a source of referral for diagnosis in one patient and aided in the rehabilitation course following treatment for both patients.
CONCLUSIONS: Hepatoblastoma is the most common primary liver tumor in children and has an increased incidence in children with a history of prematurity and very low birth weight. Providers who frequently care for the very low birth weight and premature children with CP should be aware of this correlation and include hepatoblastoma in the differential when managing patients with suddenly worsening constipation or abdominal distension. Pediatric physiatrists and other providers for these patients could be a source of referrals and diagnosis leading to timely treatment.

Keywords: Cerebral palsy, infant very low birth weight, hepatoblastoma, prematurity, birth premature, congenital cerebral palsy

1. Introduction

Hepatoblastoma is the most common primary liver tumor in children. However, the incidence is low at 0.5–1.5 cases per million children between ages of 0 and 14. It is estimated that 100 cases are diagnosed in the United States per year and the incidence of hepatoblastoma has been rising at a rate of 4% per year between 1992 and 2004 [1,14]. It most commonly affects children under the age of 4. Survival rates of localized disease in the United States are greater than 80%; in metastatic cases survival range is 20–70% three to five years after diagnosis. It is considered an embryonal tumor that develops in utero related to cell proliferation and differentiation during hepatic organogenesis. On histology hepatoblastoma cells resemble embryonal liver cells [1,15]. On clnical presentation hepatoblastoma can cause anorexia, unexplained weight loss, abdominal distention, abdominal pain, isosexual precocity, elevated liver enzymes, jaundice and constipation [2,3].

The association of hepatoblastoma with prematurity

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and very low birth weights was first noted in the scientific literature during the 1990s [4,5]. Subsequent epidemiological studies from multiple countries have shown a significantly increased rate of hepatoblastoma in very low birth weight infants (those weighing less than 1500 grams at birth) [6]. Despite the overall low incidence of hepatoblastoma, premature very low birth weight infants have a disproportionate risk of developing this tumor. The odds ratio for development of hepatoblastoma in the very low birth weight infants ranged from 9.5 in Nordic Countries to 69 in the United Kingdom [1]. The United States reported an odds ratio of 15.4–17.2 [6–8] Even the moderately low birth weight infants (1500–2500 g) have a 2 fold increase in risk [1]. When comparing very low birth weight infants' cancer risk, hepatoblastoma was the only cancer to be strongly correlated. A recent meta-analysis found that leukemia, lymphoma, primary central nervous system tumors, retinoblastoma, nephroblastoma, rhabdomyosarcoma or thyroid cancer do not show an increased risk with prematurity [9].

There is no clear cause of hepatoblastoma in very low birth weight premature infants. There is an association with maternal smoking. In 2009, the International Agency for Research on Cancer declared that parental smoking is a carcinogen to the fetal liver. Most tumors are sporadic, but one-third of cases may be associated with Beckwith-Weidemann Syndrome, familial adenomatous polyposis (FAP), Edward syndrome (trisomy 18), nephroblastoma, and Down syndrome [10,16,17].

2. Case presentation

The first case is a 6-year-old female with history of premature birth at 26-weeks gestation and spastic dystonic quadriplegic cerebral palsy with gross motor function classification scale (GMFCS) level IV, manual ability classification system (MACS) level IV, and communication function classification system (CFCS) level II. She used a power wheelchair for mobility and was dependent for transfers. She followed with pediatric rehabilitation medicine for management of spasticity and dystonia. As part of her treatment for spasticity she received intramuscular botulinum toxin injections at a dose of 12 units per kilogram. Prior toxin injections were completed more than 3 months prior to presentation, to which she had responded well, without adverse effects and improved comfort and posture. She returned to clinic 2 weeks later with worsening constipation and dystonia. Her Barry Albright Dystonia Scores had increased from three to four in the right upper extremity and the bilateral lower extremities. Constipation was refractory to treatment with oral medications. She was directed to the ER for evaluation.

Diagnostic work up was remarkable for a highly elevated alpha-fetoprotein level at 913,000 (normal 0–8.0), a mild transaminitis, a large liver mass involving the right lobe with extension to the left lobe, and 3 lung nodules. Biopsy confirmed a diagnosis of Stage IV metastatic hepatoblastoma. She received chemotherapy with cisplatin, vincristine, fluorouracil, and adriamycin. Chemotherapy was effective in shrinking the tumor and the patient underwent resection of the hepatoblastoma approximately three months after initiation of chemotherapy. Following recovery from surgery, the patient completed another three months of chemotherapy. She is currently seen annually in the long-term oncology survival clinic. She continues to follow with pediatric rehabilitation for management of her cerebral palsy.

The second case is a 3-year-old male with history of 28-weeks prematurity, periventricular leukomalacia and hydrocephalus requiring a ventriculoperitoneal shunt. He had a diagnosis of spastic diplegic cerebral palsy with GMFCS level II, MACS level I, and CFCS level I. He arrived at clinic with abdominal distention, constipation, and new onset precocious puberty. He was likewise referred to the ER for evaluation.

Work-up demonstrated a markedly elevated AFP level, a liver mass and lung nodules. He was diagnosed with Stage IV hepatoblastoma. After multiple rounds of chemotherapy, he returned to the hospital for resection of the tumor and liver transplantation. Hospital course was complicated by shunt malfunction, and postoperative bleeding and infection. He received inpatient rehabilitation prior to discharge home. He remains under surveillance with oncology and transplant teams for disease recurrence. He continues to follow with pediatric rehabilitation for management of his cerebral palsy.

3. Discussion

Cerebral Palsy (CP) risk increases with declining gestational age at birth. Infants born prior to 28 weeks' gestation have approximately 50 times the risk of full term infants for being diagnosed with CP [11]. The CP population frequently is managed by pediatricians, neurologists and physiatrists, who often treat secondary complications such as constipation. Constipation af-

Table 1
Differential diagnosis of constipation in the CP population

System	Differential diagnosis
CNS	– Cerebral Palsy affecting motility
	– Encephalopathy
	– Spinal Cord Injury
	– Spasticity
GI	– Diet – poor fiber intake
	– Tube Feeding
	– Cow's milk intolerance
	– Dehydration
	– Bowel Obstruction
	– Anatomic Malformation
	– Hirschprung's disease
	– Abdominal tumor
Metabolic	– Hypothyroidism
	– Hypercalcemia
	– Hypokalemia
	– Celiac disease
Connective tissue disorder	– Scleroderma
	– Systemic lupus erythematosus
Iatrogenic	– Oral medication side phenobarbital, opioids
	– Botulism

fects a significant proportion of the CP population, with estimates between 26–74% depending upon how constipation is defined and the population studied [12]. The differential diagnosis of constipation and abdominal distension in the premature/cerebral palsy population is broad. Table 1 presents a differential diagnosis by systems of constipation in the cerebral palsy population.

Patients who present with new or suddenly worsening constipation may require a more thorough work up of symptoms. This approach should be considered on patients who fail to respond to conservative management or develop other red flag symptoms. Red flag symptoms include suddenly worsening constipation, increased abdominal girth or distension. Recent onset constipation that persists and does not respond to conservative treatment should be evaluated for abdominal masses that may cause bowel obstruction [13]. Further work up may include an abdominal ultrasound or screening labs such as liver function tests, alpha fetoprotein level, complete blood count and coagulation markers. Referral to a pediatric oncology and surgical team is paramount if hepatoblastoma is found.

Although hepatoblastoma is a rare tumor found in childhood, the risk is greatly increased if the child was premature and born at a very low birth weight. These case reports emphasize hepatoblastoma in the setting of prematurity and very low birth weight infants for patients with cerebral palsy. They each presented with acutely worsening constipation and abdominal distension. Referral for evaluation of the constipation led to timely diagnosis. Both patients experienced good outcomes. Physicians who commonly manage patients with cerebral palsy should be aware of this correlation. Constipation is a common chronic problem for children with CP. Pediatric physiatrists and pediatricians who manage constipation should be aware of this correlation and maintain a high index of suspicion for reports of a change in the pattern of constipation.

Conflict of interest

The authors have no conflicts of interest to report.

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