CPQ Cancer (2018) 1:4
Review Article

Infantile Hepatic Hemangioendothelioma, A Review of Literature

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Received: 11 October 2018

Published: 14 November 2018

Keywords: *Infantile; Hemangioendothelioma; Cardiovascular Complications*

Abstract

Despite its rarity, Infantile hepatic hemangioendothelioma (IHHE) is the most common hepatic vascular tumor in children [1]. According to the International Society for the Study of Vascular Anomalies (ISSVA) classification, lesions can be classified into focal, multifocal and diffuse [2]. While hepatomegaly is the most common presenting feature, IHHE may be accompanied by cardiovascular complications, coagulopathies, hypothyroidism, and angiomatous and non-angiomatous lesions [3-8]. Depending on the presentation and associated morbidities, treatment options include observation, medical treatment and/or surgical resection. In rare occasions, liver transplantation might be considered [2,9-13].

Introduction

Infantile hepatic hemangioendothelioma (IHHE) is the most common vascular tumor in the liver in pediatric age group [1]. Most cases are diagnosed in the first 2 months of age (85%) and it is rare after the age of 3 years [14].

While IHHE is benign in nature, it is frequently associated with several morbidities (i.e. visual, respiratory and gastrointestinal) that might necessitate medical intervention. Moreover, life threatening conditions such as congestive heart failure was reported with this disease [15].

Treatment options for IHHE vary widely depending on patients' presentation and any associated morbidities. Spontaneous regression within a year is almost always the natural course for asymptomatic lesions. While oral steroid is the most widely used treatment, interferon alpha and propranolol are other available treatment options [13,16,17]. Other more invasive treatment modalities include hepatic artery embolization, hepatic artery ligation, resectional surgery and liver transplantation might also be considered in symptomatic cases or those with associated complications [18].

Epidemiology, and Demographics

IHHE accounts for around 12% of all pediatric hepatic tumors [19-21]. IHHE has a female predominance with a male to female ratio of 1:1.3-2. It has a higher incidence in preterm infants, and Caucasian population [22-26].

Classification & Clinical Presentation

The International Society for the Study of Vascular Anomalies (ISSVA) classification is the most commonly used classification. IHHE is classified into focal, multifocal and diffuse lesions based on the extent of unaffected liver parenchyma [2,26]. (Table 1)

Table 1: *Comparison of different types of IHHE*

	Focal lesions	Multifocal lesions	Diffuse lesions
Development	Completely formed at birth	Develop postnatally	Develop postnatally
GLUT-1 staining	Negative	Positive	Positive
MRI findings	• Single mass • Hypointense on T1 and hyperintense on T2 • Calcification and cystic changes may be present	• Spherical masses • Hypointense T1 and hyperintense on T2 • Rapid enhancement	• Many lesions replacing almost all liver parenchyma • Hyperenhancement

CT findings	• Rapid enhancement • Calcification and cystic changes may be present	• Uniform or centripetal	• Many lesions replacing almost all liver parenchyma • Rapidly enhancing
Association with cutaneous hemangiomas	In > 15%	In > 60%	Frequent
Complications	• Mild thrombocytopenia • Arteriovenous shunting	• Moderate cardiomegaly • High-output heart failure	• High output heart failure • Respiratory distress • Abdominal compartment syndrome • Multiorgan system failure •Severe hypothyroidism

Most of the focal IHHE are asymptomatic, while multifocal and diffuse types are often symptomatic [2]. Clinical features of solitary lesions depends on the tumor size and the volume of shunted blood [27]. While, patients with multifocal IHHE frequently present with hepatomegaly (83%), upper abdominal mass (66%), cardiovascular failure, coagulopathy and/or jaundice [3,28]. Less common manifestations include vomiting, splenomegaly, ascites, gastrointestinal bleeding, anemia, feeding difficulties and hepatic bruits [3,29].

Cardiovascular Complications

Due to arteriovenous shunting, IHHE can cause high output congestive heart failure particularly with multifocal tumor. Cardiac failure may be the initial presentation which may misleadingly be attributed to congenital heart disease [3,30-33]. As arteriovenous shunts are perfused from the hepatic artery, those patients can be treated with hepatic artery ligation [34].

Coagulopathy

Coagulopathy that complicates IHHE is seen more frequently with multifocal IHHE [3]. It can be secondary to activation and consumption of coagulation factors in a similar manner as with highly vascular tumor (Kasabach-Merritt syndrome) [35-40].

Hypothyroidism

IHHE associated consumptive hypothyroidism was first reported by Huang *et al.* in 2000 [4]. Type 3 iodothyronine deiodinases produced by the tumor converts T4 and T3 to inactive metabolites. There is a direct relationship between the incidence of hypothyroidism and the growth pattern of the tumor. It is more common with diffuse IHHE and to a lesser extent with multifocal IHHE. Interestingly, this complication regresses with regression of the tumor size or with liver transplant [6,41-43]. Since undetected hypothyroidism can cause a permanent neurologic damage, defective hemostasis and cardiac symptoms, it is crucial to monitor thyroid hormone levels when diffuse IHHE is diagnosed [26,44].

Cutaneous Angiomas

Cutaneous angiomas are commonly associated with IHHE (50% of patients) [5,45]. Kulungowski *et al.* reported an incidence of 77.4% with multifocal IHHE, 53.3% with diffuse type and 15.3% with focal type [6].

Non-Angiomatous Tumors

IHHE associated hepatic mesenchymal hamartomas may cause elevation in serum alpha-fetoprotein. In addition, large brain hemangiomas that may be associated with multicentric IHHE have been reported [7,8,46,47].

Diagnosis of IHHE

Imaging Studies

Multiple imaging modalities may be used for diagnosis and surveillance of IHHE including sonography, CT, monitoring tumor's growth and MRI.

Sonography

Sonography is useful in detecting fetal hepatic hemangioendothelioma as well as monitoring tumor's growth pattern and treatment response [48-52]. Characteristic features include complex heterogenous hypoechoic masses, with occasional calcifications that can be attributed to central hemorrhage, necrosis, or fibrosis of the lesion. The solitary lesions appear as round nodules consisting of tortuous markedly perfused cavities while multifocal lesions may present as a solid tumor.

Computed Tomography (CT)

On non-contrast CT, IHHE appears as multiple hypo-attenuated well-demarcated nodules or masses, more frequently in the periphery. Dynamic scans that use intravenous contrast material may show peripherally enhanced lesions with no central enhancement. On delayed scans, a washout of the peripheral enhancement and filling in of the center of the lesion can be seen. This is because of the slower blood flow within the lesion compared to the rest of the liver [53]. Small lesions may show central enhancement initially which may be considered equivalent to peripheral enhancements in large lesions [54]. Three Criteria were suggested for diagnosis of hemangioma by Freeny and Marks which are diminished attenuation in non-contrast CT, peripheral enhancement in dynamic CT and complete iso-attenuating filling of the lesion in delayed scans [55].

Magnetic Resonance Imaging (MRI)

Hemangiomas appear as hypointense lesions in T1 weighted images and markedly hyperintense in T2 weighted images [56]. If fibrosis is present within the lesion, it appears as areas of hypointensity in a

hyperintense lesion [57]. While if there are cystic changes or hemorrhage, it appears as areas of increased signal intensity compared to the already hyperintense lesion in T2 weighted images [56]. MR imaging has some limitations even with contrast administration as they cannot consistently differentiate hemangiomas from some other lesions especially hypervascular malignancies [58].

Differential Diagnosis

On diagnosis of IHHE, there are other rare tumors that need to be excluded. One example is Kaposiform hemangioendothelioma which has a more infiltrative nature and usually accompanied by Kasabach Merritt syndrome. Although it presents in older children, undifferentiated embryonal sarcoma should also be included in the differential diagnosis. Angiosarcoma is another rare diagnosis in infants that should be included in the differential diagnosis as it can mimic IHHE on imaging.

IHHE should be differentiated from hepatoblastoma that may occur in the same age group. Imaging can be helpful in differentiating it from IHHE as hepatoblastoma appears heterogenous in T2 weighted MRI sequence. Other benign lesions that may resemble IHHE include cysts, arteriovenous malformations and biliary hamartomas [3,26].

Management of IHHE

The treatment of IHHE depends on the clinical presentation and the asociated complications [9]. Since focal IHHE mostly involutes spontaneously, no treatment is usually needed. In rare cases that are associated with arteriovenous shunting, embolization may be considered.

Multifocal and diffuse IHHE types are usually symptomatic and often require medical, interventional, or surgical management. Historically, oral corticosteroids have been the main medical treatment for problematic multifocal and diffuse IHHE [10]. The efficacy of corticosteroids in terms of stabilization or reducing tumor size were as high as 75%. The used doses ranged from 2-3 mg/kg/day. Despite all published reports, there is no standard regimen regarding the optimal dose and tapering regimen for corticosteroids [10,59]. Treatment with corticosteroids carried many side effects including hyperglycemia, hypertension, growth retardation, Cushing syndrome and immunosuppression [60]. Even after 2008, when propranolol was proved highly effective in inducing involution of infantile hemangiomas, many published studies still used interferon 2 alpha and corticosteroids for treatment of IHHE. Interferon 2 alpha is estimated to cause spastic diplegia in around 2.5% of infantile hemangioma patients and was also associated with motor developmental disturbance in another 4.1% [61].

Propranolol, a nonselective beta blocker, dramatically changed the treatment approach since the discovery of its efficacy in treating infantile hemangiomas. While the exact mode of action of propranolol in IHHE is not totally clear, multiple hypotheses have been discussed including vasoconstriction, inhibition of angiogenesis, decreased renin production and stimulation of apoptosis [62-64]. Compared to corticosteroids, propranolol carried a more rapid and greater response. Several reports demonstrated the efficacy of propranolol (in a dose of 2-3mg/kg/day) in controlling the proliferation of IHHE [65-67]. Few studies demonstrated the efficacy of propranolol in combination with corticosteroids in treating IHHE [13,68,69].

The use of propranolol in patients with IHHE has its side effects. These include bradycardia, hypotension, hypoglycemia, and exacerbation of bronchospasm [67].

Other medical treatments including vincristine and cyclophosphamide have shown various degrees of success [2,11,69].

Surgical resection and hepatic artery embolization were the main treatment options for IHHE before the efficacy of medical treatment was proven [12]. Currently, surgery is rarely performed for IHHE and is usually reserved as a last resort in problematic cases that are refractory to medical treatment. With the refractory cases specially presenting with abdominal compartment syndrome, a liver transplant may be indicated [13].

Conclusion

Despite the benign nature of IHHE, some cases may require aggressive treatment, especially in multifocal and diffuse types. Propranolol is considered the golden treatment for IHHE, considering the fewer side effects it carries compared to the long-term use of corticosteroids. While the treatment of IHHE has much evolved in the last decade, understanding the nature of IHHE may lead to a revolution in the currently used treatment modalities. Considering the rarity of the disease, prospective multicentric trials should be the ultimate goal to reach consensus on the management algorithm of IHHE including imaging techniques, treatment regimens and doses, the period of follow up and treatment options in recurrence.

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