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Review Article

Congenital hepatic hemangioma: a review

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ABSTRACT

Congenital hepatic hemangioma (CHH) is a benign vascular malformation of the liver observed in newborns. Despite its rarity, it is crucial to understand its clinical presentation, diagnosis, and management due to potential complications. This extensive bibliographic review compiles key references to provide a detailed overview of the epidemiology, pathogenesis, clinical manifestations, diagnostic methods, and therapeutic options for CHH, aiming to offer a comprehensive insight into this condition.

Keywords: Hemangioma, CHH, Hepatic hemangioma, Congenital, Vascular surgery, Endovascular surgery

INTRODUCTION

Congenital hepatic hemangiomas (CHH) are benign vascular tumors of the liver detected primarily in the neonatal period. Unlike other congenital hemangiomas, CHH can present a variety of symptoms, ranging from asymptomatic to severe complications such as congestive heart failure, coagulopathies, and hemorrhages. Specific management is essential to prevent these complications.[1]

Precise classification of CHH and differentiation from other hepatic vascular malformations is fundamental for guiding clinical management. For instance, hepatic arteriovenous malformations may require completely different therapeutic approaches compared to CHH.[1,2]

The International Society for the study of vascular anomalies (ISSVA) has developed a detailed classification of vascular anomalies, updated in 2024 to reflect recent advances in understanding these conditions. The ISSVA classification divides vascular anomalies into two main categories: vascular tumors and vascular malformations.[2]

CHH is classified as a congenital hemangioma within the vascular tumors category. Unlike infantile hemangioma, which appears postnatally and follows a characteristic course of rapid proliferation followed by involution, CHH is present at birth and can exhibit different clinical patterns, such as rapid involution (RICH) or non-involution (NICH).[1,3]

The incidence of CHH is low, estimated at approximately 1 in 20,000 live births, with a higher prevalence in females. Genetic and environmental factors, including mutations in angiogenesis-regulating genes and conditions during fetal development, play significant roles in its pathogenesis.[4]

Diagnosis of CHH relies on imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), and in some cases may require liver biopsy. Treatment may include medications like propranolol, surgical interventions, and endovascular techniques such as arterial embolization.[1,3,4] Continued research is vital to improve treatment options and reduce associated complications.

CLASSIFICATION

The classification of CHH can be better understood by considering several aspects such as hemangioma involution, ISSVA classification, and criteria based on tumor size and extent.[1,3]

Classification by involution

Rapid involution congenital hemangioma (RICH) are hemangiomas that show a rapid decrease in size during the first months of life.[5]

Non-involuting congenital hemangioma (NICH) are hemangiomas that do not show a significant decrease in size over time.[4,5]

ISSVA classification

The recent ISSVA classification, published in 2024, categorizes hemangiomas within "vascular tumors", distinguishing between: infantile hemangiomas which appear postnatally and have a growth cycle followed by involution, and congenital hemangiomas which are present at birth, with variants that either rapidly involute or do not involute.[2,3,5]

Classification by size and extent

According to Mulliken et al, CHH can be classified by size and extent - small: generally, less than 2 cm, asymptomatic, and often do not require intervention, moderate: between 2 cm and 5 cm, may require monitoring due to the risk of complications, large: over 5 cm, with a higher risk of causing symptoms or complications such as congestive heart failure and coagulopathies, and diffuse or multifocal: hemangiomas that encompass a large part of the liver or present multiple nodes, involving more complex clinical management.[1]

EPIDEMIOLOGY

CHH is one of the most common forms of liver tumors in neonates, although it remains a rare condition.[1,6] The incidence and prevalence of this condition are low, but studying it is crucial to improve diagnosis and clinical management.

Relevant studies on the incidence, prevalence, risk factors, and demographic distribution of CHH will be described to provide a comprehensive understanding of its epidemiology.

Incidence

The incidence of CHH is estimated at approximately 1 in 20,000 live births, although this figure may vary slightly depending on the region and access to advanced diagnostic techniques.[5]

Prevalence

Studies suggest a higher prevalence in females compared to males, with a ratio of approximately 2:1.[6,7]

Risk factors

Genetic and environmental factors

While the exact etiology of CHH is not fully understood, both genetic and environmental factors are believed to play significant roles in its development. Studies suggest a possible association with certain genetic syndromes and vascular malformations.[5,7]

Demographic distribution

Sex and age

CHH is primarily detected in the neonatal period, with a higher prevalence in females. Prenatal imaging studies have improved early detection, allowing more effective management of the condition.[8,9]

Race and ethnicity

Reviewed literature does not show significant differences in the prevalence of CHH among different racial or ethnic groups, although most studies have been conducted in Western populations.[9]

PATHOGENESIS

Understanding its pathogenesis is crucial for developing effective diagnostic and treatment strategies. This review aims to explore the pathogenic mechanisms involved in the formation of CHH, including genetic factors, abnormalities in vascular development, and the contribution of environmental factors.

Genetic factors

Genetics and associated syndromes

Some studies have identified a possible genetic predisposition to the development of CHH. For example, mutations in genes regulating angiogenesis, such as vascular endothelial growth factor (VEGF) and tyrosine kinase with immunoglobulin-like and EGF-like domains (TIE2), may play a significant role in its pathogenesis.[10,11] Additionally, CHH may be associated with genetic syndromes such as Klippel-Trenaunay syndrome.[12]

Family and twin studies

The occurrence of CHH in monozygotic twins suggests a genetic basis for the disease. Family studies have also demonstrated a higher incidence of CHH in families with a history of vascular malformations.[13]

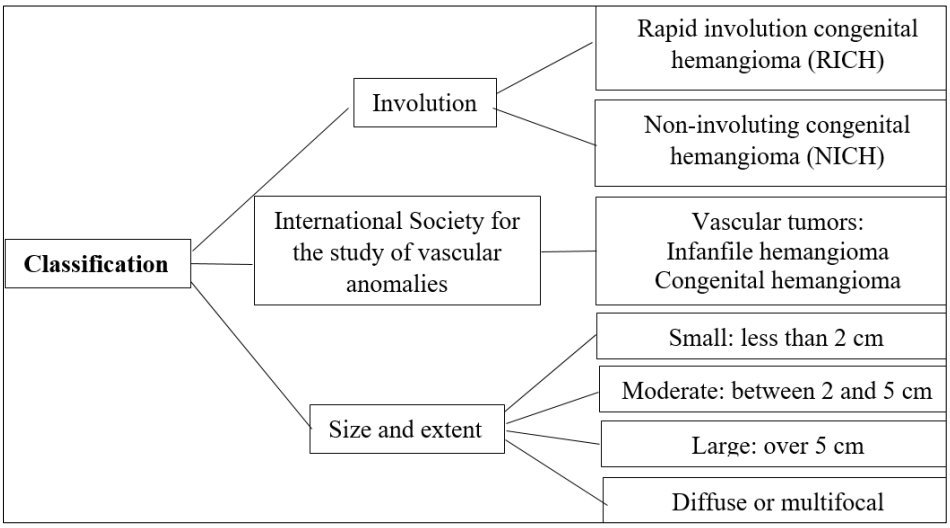

Figure 1: Classification of congenital hepatic hemangioma.

Vascular development abnormalities

Fetal vascular development

CHH is believed to result from abnormalities in fetal vascular development. During embryonic development, deregulated angiogenesis can lead to hemangioma formation.

The abnormal expression of angiogenic growth factors such as VEGF and FGF plays a crucial role in this process.[12,14]

Hypoxia and angiogenesis

The hypoxia hypothesis suggests that tissue hypoxia during fetal development may trigger compensatory angiogenesis, resulting in hemangioma formation. Studies have shown elevated levels of HIF-1α in hemangiomas, indicating a response to hypoxia.[15,16]

Molecular and cellular factors

Endothelial proliferation

Hepatic hemangiomas are characterized by excessive endothelial cell proliferation. This proliferation is mediated by abnormal angiogenic signals, including the overexpression of VEGF and other endothelial growth factors.[10,11,14]

Tumor microenvironment

The tumor microenvironment, including inflammatory cells and the extracellular matrix, also plays an important role in CHH pathogenesis. The interaction between endothelial cells and the microenvironment can promote tumor cell proliferation and survival.[12,14,15,17]

Environmental factors

Maternal influence

Environmental factors such as maternal infections and exposure to toxins during pregnancy can influence CHH pathogenesis. Exposure to teratogenic factors may alter fetal vascular development, contributing to hemangioma formation.[12,15]

Hormones

Hormones, particularly estrogens, can influence the growth of CHH. The high incidence of CHH in females suggests a possible role of sex hormones in its development.[15,18] The pathogenesis of congenital hepatic hemangioma is multifactorial, involving a complex interaction of genetic factors, vascular development abnormalities, and environmental contributions. Understanding these mechanisms is essential for developing more effective treatment protocols and diagnostic strategies. Future research should focus on unraveling the specific molecular pathways and genetic factors contributing to this disease.

CLINICAL PRESENTATION

The identification and management of CHH can be challenging due to variability in its clinical presentation. Understanding the clinical manifestations and potential complications is crucial for effective treatment.

Clinical manifestations

Asymptomatic

Many cases of CHH are asymptomatic and discovered incidentally during imaging studies conducted for other reasons.[1,3,19]

Palpable abdominal mass

A common presentation of CHH is a palpable abdominal mass. In some cases, this may be the only clinical manifestation.[7,20]

Congestive heart failure

CHH can cause congestive heart failure due to a significant arteriovenous shunt within the tumor, leading to increased venous return to the heart.[21]

Hepatomegaly

Hepatomegaly is a frequent manifestation in patients with CHH, especially when tumors are large or multiple.[20,22]

Jaundice

In cases where CHH causes biliary obstruction or cholestasis, patients may present with jaundice.[19,20]

Complications

Kasabach-Merritt syndrome

This syndrome, characterized by thrombocytopenia and consumptive coagulopathy, can be associated with CHH, especially in large or multifocal tumors.[23,24]

Intra-abdominal hemorrhage

Although rare, intra-abdominal hemorrhage is a potentially life-threatening complication of CHH.[25]

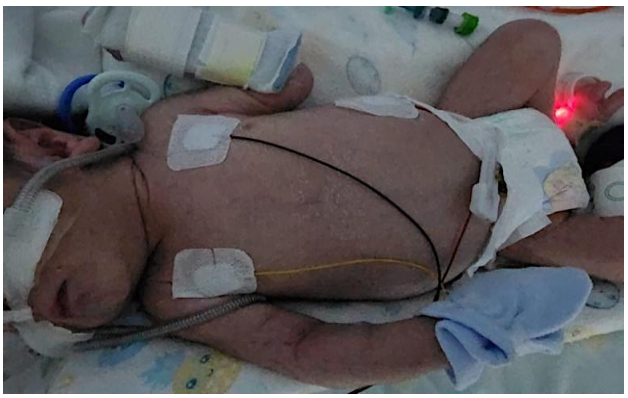

Figure 2: Clinical findings of a newborn with hepatomegaly and collateral veins in abdomen.

DIAGNOSIS AND DIAGNOSTIC METHODS

Diagnosis of CHH can be challenging due to variability in its clinical presentation and imaging characteristics. Accurate diagnosis and characterization are essential for appropriate management. This review focuses on available diagnostic methods, including imaging techniques and invasive procedures, and provides a detailed overview of their applications and limitations.

Diagnostic imaging methods

Ultrasound (US)

Ultrasound is generally the first diagnostic method used to detect CHH due to its availability and safety. This method can reveal a hyperechoic hepatic mass, although sensitivity and specificity may vary.[24]

Computed tomography (CT)

CT is useful for further evaluation of hepatic masses detected by ultrasound. It provides details on the tumor's structure and vascularization and is useful for planning surgical interventions.[6,26]

Magnetic resonance imaging (MRI)

MRI is the preferred technique for the detailed characterization of CHH. It offers excellent soft tissue resolution and is particularly useful for evaluating the tumor's relationship with vascular and biliary structures.[22,27]

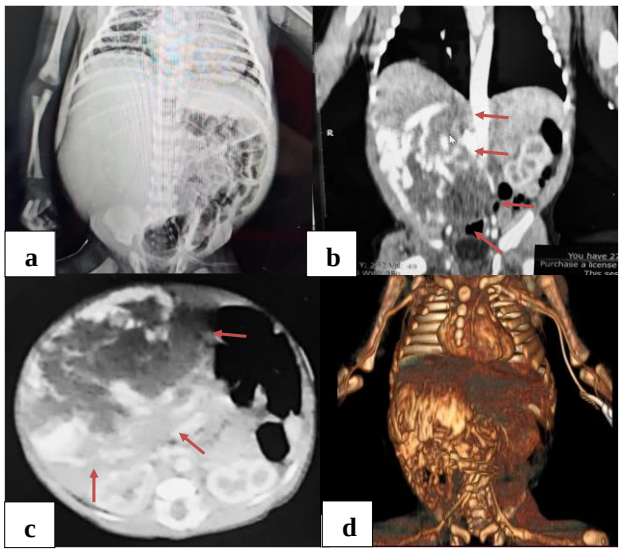

Figure 3: Diagnostic imaging methods suggestive of CHH (a) X-ray showing evidence of hepatomegaly in a newborn, and (b-d) axial, coronal, and reconstructed images from an angio-CT scan suggestive of CHH.

Invasive diagnostic methods

Liver biopsy

Liver biopsy is reserved for cases where the diagnosis is unclear with imaging techniques. It can provide a definitive histopathological diagnosis, although it is associated with risks of complications.[25]

Advanced techniques and functional evaluation

Angiography

Angiography can be used in complex cases to assess CHH vascularization and plan therapeutic interventions such as embolization.[11,18,21]

Positron emission tomography (PET)

Although not routine, PET can be useful in selected cases to assess the tumor's metabolic activity and differentiate between benign and malignant lesions.[16,24,26]

Clinical evaluation

Medical history and physical examination are fundamental for the initial evaluation and follow-up of patients with CHH. Symptoms such as hepatomegaly, jaundice, and heart failure can indicate the need for additional studies.[7,19]

The diagnosis of congenital hepatic hemangioma requires a combination of imaging techniques and, in some cases, invasive procedures to obtain a definitive diagnosis. The choice of diagnostic method depends on the patient's clinical presentation and the availability of techniques.

Table 1: Diagnostic methods for CHH: advantages and disadvantages.

Diagnostic method	Advantages	Disadvantages
Ultrasound (US)	Non-invasive	Operator-dependent
	Safe and accessible	Difficulty in characterizing complex masses
Computed tomography (CT)	Good spatial resolution	Radiation exposure
	Useful for assessing the extent of the lesion	Possible need for intravenous contrast
Magnetic resonance imaging (MRI)	Does not use ionizing radiation	Prolonged examination time
	Excellent soft tissue characterization	Need for sedation in neonates
Liver biopsy	Definitive diagnosis	Invasive procedure with risk of bleeding
Angiography	Detailed evaluation of tumor vascularization	Invasive and associated with risks of vascular complications
Positron emission tomography (PET)	Functional evaluation of the tumor	Limited availability
		High cost
Clinical evaluation	Easy to perform	Subjective
	Non-invasive	Dependent on clinician's experience

MEDICAL, SURGICAL, AND ENDOVASCULAR TREATMENT

The treatment of CHH varies according to the patient's clinical presentation, symptom severity, and presence of complications. Its management requires a comprehensive understanding of the available treatment options, including medical therapies, surgical interventions, and endovascular procedures.

Medical treatment

Propranolol

Propranolol, a non-selective beta-blocker, has become a first-line treatment for infantile hemangiomas due to its efficacy in reducing tumor size and relieving symptoms. Propranolol induces vasoconstriction, decreases cell proliferation, and promotes apoptosis of hemangioma cells. Studies have shown a high success rate in reducing CHH size and improving symptoms.[3,10,11,18]

Corticosteroids

Corticosteroids, such as prednisolone, act by reducing inflammation and decreasing endothelial cell proliferation. They have been historically used to treat CHH, although their use has decreased with the introduction of propranolol. Clinical evidence shows a lower success rate and higher incidence of side effects compared to propranolol.[28]

Interferon alpha

Interferon alpha has been used in cases resistant to other treatments, although its use is limited due to side effects from neurotoxicity and other significant adverse effects. Interferon alpha inhibits angiogenesis and endothelial cell proliferation.[29]

Surgical treatment

Surgical resection

Surgery may be necessary in symptomatic CHH cases that do not respond to medical treatment or in the presence of severe complications such as bleeding or heart failure. Indications for surgical treatment include large tumors (greater than 5 cm), hemorrhagic complications, and cases resistant to medical treatments. Complete resection of the hemangioma can cure the disease but carries significant surgical risks.[1,11,17,30]

Endovascular treatment

Arterial embolization

Arterial embolization is an endovascular technique used to reduce blood flow to the hemangioma, promoting tumor regression. In CHH with severe symptoms or complications, particularly in cases where surgery is not viable, it has shown high efficacy in reducing hemangioma size and improving symptoms, although with possible complications such as hepatic necrosis.[3,30,31]

New therapies and experimental treatments

Sirolimus therapy

Sirolimus, an mTOR pathway inhibitor that reduces cell proliferation and angiogenesis, has shown promise in treating CHH, especially in complicated or treatment-resistant cases. Preliminary studies indicate efficacy in reducing hemangioma size and improving symptoms, although further research is needed.[3,31-33]

Surveillance and observation

The treatment of CHH may include surveillance and observation in certain cases. This approach avoids invasive procedures and the associated risks, such as hemorrhages or infections and it is particularly relevant for asymptomatic hemangiomas or those of small to moderate size that do not present immediate complications. The decision to opt for surveillance and observation is based on the clinical evaluation of the patient, the severity of symptoms, and the potential risk of complications.[1,5,7,24]

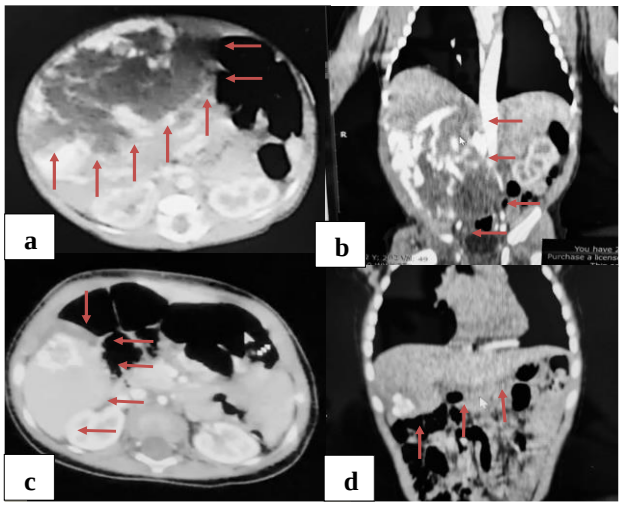

Figure 4: Comparative CT scan at 10 months showing evidence of involution of the CHH managed with observation and surveillance, (a) and (b) evidence of gigantic CHH in newborn by CT scan, and (c) and (d) involution after 10 months of observation and surveillance.

Table 2: Treatment comparison: medical treatment versus open surgery versus endovascular for congenital hepatic hemangioma.

Aspect	Medical treatment	Open surgery	Endovascular treatment
Procedure type	Use of medications such as propranolol, corticosteroids, interferon alpha	Resection of the hemangioma through an open surgical approach	Minimally invasive techniques such as arterial embolization
Indications	Small to moderate hemangiomas, initial treatment for symptomatic cases	Large tumors (>5 cm), severe symptoms, hemorrhagic complications	Moderate-sized hemangiomas, failure of medical management, severe symptoms
Advantages	Non-invasive, lower risk, can be effective in reducing tumor size	Definitive removal of the hemangioma, potential for complete cure	Less invasive, lower immediate postoperative risk, shorter recovery time
Risks	Side effects from medications (e.g., bradycardia, hypertension, neurotoxicity)	Surgical risks including bleeding, infection, longer recovery period	Risk of hepatic necrosis, potential for incomplete treatment, recurrence
Recovery time	Generally does not require hospital stay; outpatient management	Longer hospital stay and recovery period, typically several weeks	Shorter hospital stay, quicker recovery, often within days
Effectiveness	Effective for many cases, especially with propranolol; variable with other drugs	High effectiveness for complete removal; low recurrence if fully resected	Effective for reducing size and symptoms; risk of recurrence
Complications	Potential for medication-related complications; ongoing monitoring needed	Higher risk of major complications such as liver dysfunction, infections	Lower risk of major complications; potential for vascular complications
Suitability	First-line treatment especially those that are asymptomatic or mildly symptomatic	Suitable for patients with tumors unresponsive to other treatments	Suitable for patients who are high-risk surgical candidates

CONCLUSION

Congenital hepatic hemangioma, although rare, requires a deep understanding for adequate management. Most cases do not need intervention, but in complicated cases, managing congenital hepatic hemangioma requires a multidisciplinary approach that includes medical, surgical, and endovascular therapies. The choice of treatment depends on clinical presentation, symptom severity, and response to initial treatments. Continuous research is necessary to better understand pathogenesis, improve and develop more effective treatments, and reduce associated complications.

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REFERENCES

1. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: A classification based on endothelial characteristics. Plast Reconst Surg. 1982;69(3):412-22.
2. International Society for the Study of Vascular Anomalies. ISSVA Classification for Vascular Anomalies 2024. Available at: https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf. Accessed on 12 May 2024.
3. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, Guibaud L, Baselga E, Posiunas G, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med. 2015;372(8):735-46.
4. Walter JW. Genetic and molecular insights into the development of vascular anomalies. J Pediatr. 2000;136(6):814-20.
5. Alario AJ, Laufer MR. Congenital hepatic hemangiomas: A review. J Pediatr Surg. 2001;36(8):1241-6.
6. Daltro P, Fricke BL, Kline-Fath BM. Imaging of fetal hepatobiliary anomalies. Pediatr Radiol. 2010;40(6):1015-25.
7. Finegold MJ. Tumors of the liver in infants and children: A review. Pediatr Pathol Mol Med. 2003;22(5):441-60.
8. Gresham TL, Smith AE. Congenital hepatic hemangiomas and infantile hemangioendotheliomas: Diagnosis and management. Semin Pediatr Surg. 2009;18(4):211-20.
9. Hedberg J. Hepatic hemangioma in the neonate: Clinical and imaging features. Am J Roentgenol. 2005;185(4):782-89.
10. Hogeling M, Adams S. Propranolol for the treatment of hemangiomas in children. Canad Fam Phys. 2012;58(2):173-5.
11. Greene AK, Rogers GF, Mulliken JB, Fishman SJ. Management of congenital hemangiomas: The role of surgery. J Pediatr Surg. 2012;47(1):81-7.
12. Boye E, Yu Y, Paranya G, Mulliken JB, Olsen BR, Bischoff J. Clonality and altered behavior of endothelial cells from hemangiomas. J Clin Investig. 2001;107(6):745-52.
13. Stevenson DA, Birch PH. Vascular anomalies and genetic syndromes. J Med Genet. 2007;44(9):578-85.
14. Bischoff J. Progenitor cells in infantile hemangioma. J Craniofac Surg. 2009;20(1):695-97.
15. Holmgren C, Fredrikson M, Källén K, Tiderius CJ. Risk factors for hemangiomas: A case-control study. Pediatr Dermatol. 2011;28(6):687-93.
16. Kleinman ME, Greives MR, Churgin SS, Blechman KM, Chang EI, Ceradini DJ, et al. Hypoxia-induced mediators of stem/progenitor cell trafficking are increased in children with hemangioma. Arteriosclerosis Thrombosis Vasc Biol. 2007;27(12):2664-70.
17. Mulliken JB, Fishman SJ, Burrows PE. Vascular anomalies. Curr Problems Surg. 2004;41(8):577-619.
18. Maguiness SM, Frieden IJ. Current management of infantile hemangiomas. Semin Cutaneous Med Surg. 2010;29(2):106-14.
19. Burrows PE, Laor T, Paltiel HJ, Robertson RL. Diagnostic imaging in the evaluation of vascular birthmarks. Dermatol Clin. 1998;16(3):455-88.
20. Lonergan GJ, Schwab CM, Suarez ES, Carlson CL. Pediatric liver masses: Radiologic-pathologic correlation part 1. Benign tumors. Radiographics. 1998;18(2):419-48.
21. Roebuck DJ, Liu ES. Pediatric hepatic tumors: The role of interventional radiology. Pediatr Radiol. 2002;32(7):502-10.
22. Schenk JP, Euler HH, Schadmand S, Gössmann H, Wenz W. Congenital hepatic hemangiomas: MR imaging findings with clinical correlation. J Magnetic Resonance Imaging. 2003;18(6):834-41.
23. Mulliken JB, Enjolras O. Congenital hemangiomas and infantile hemangioma: Missing links. J Am Acad Dermatol. 2004;50(6):875-82.
24. Johnson CM, Navarro O, Ghazarian D. Hepatic hemangiomas in neonates: Imaging findings. Am J Roentgenol. 2000;174(5):1201-6.
25. Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, Horii KA, et al. Prospective study of infantile hemangiomas: Clinical characteristics predicting complications and treatment. Pediatrics. 2006;118(3):882-7.
26. Dubois J, Garel L, Grignon A, Yazbeck S. Imaging of liver hemangiomas in children. Pediatr Radiol. 2007;37(12):1201-10.
27. Kim HJ, Choi BI, Han JK. Congenital hepatic hemangiomas: MR imaging findings with histopathologic correlation. Korean J Radiol. 2011;12(6):728-33.
28. Blei F, Walter J, Orlow SJ, Marchuk DA, Burrows PE. Treatment of hemangiomas with systemic corticosteroids: Initial response and long-term results. J Pediatr. 2000;136(6):815-20.
29. Tan ST, Itinteang T, Day DJ, O'Donnell C. Treatment of hemangiomas with interferon-alpha:

Experience in 27 patients. J Pediatr Surg. 2000;35(11):1442-8.
30. Mackinlay GA, Gray DW. Surgical management of neonatal liver hemangiomas. J Pediatr Surg. 2006;41(3):693-8.
31. Hammer J, Seront E, Duez S, Dupont S, Van Damme A, Schmitz S, et al. Sirolimus for the treatment of complicated vascular anomalies in children. J Pediatr Hematol Oncol. 2011;33(4):314-8.
32. Adams DM, Trenor CC, Hammill AM, Vinks AA, Patel MN, Chaudry G, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. Pediatrics. 2016;137(2).
33. Triana P, Dore M, Cerezo VN, Cervantes M, Sánchez AV, Ferrero MM, et al. Sirolimus in the treatment of vascular anomalies. Eur J Pediatr Surg. 2017;27(01):86-90.

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