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Hepatic vascular anomalies in infancy: A twenty-seven-year experience

[Original Article]

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Outline

Abstract

Objective: Infantile hemangioma and arteriovenous malformation (AVM) of the liver have a similar presentation but a different natural history, and therefore require different treatment. This study was undertaken to clarify differential diagnosis and management of these two biologically distinct vascular disorders.

Study design: We retrospectively analyzed the records of 43 children with hepatic vascular anomalies treated during the past 27 years.

: Ninety percent were hemangiomas (n = 39); 10 percent were AVM (n = 4). Infants with AVM or large solitary hemangioma had hepatomegaly, congestive heart failure, and anemia as presenting symptoms at birth. Multiple hepatic hemangiomas
manifested at 1 to 16 weeks of age with the same clinical triad, plus multiple cutaneous lesions (19/23). The mortality rate after treatment of hepatic AVM was 50 percent (2/4). The mortality rates after treatment of liver hemangiomas were as follows: resection of solitary lesions, 20 percent (2/10); embolization, 43 percent (3/7); corticosteroids, 30 percent (3/10); and interferon alfa-2a, 15 percent (2/13).

Conclusion: Solitary hepatic hemangioma cannot always be distinguished from hepatic AVM without radiologic studies. Multiple hepatic hemangiomas are differentiated from hepatic AVM by coexistence of multiple cutaneous hemangioma and by radiologic imaging. We recommend combined embolization and surgical resection for hepatic AVM and for solitary symptomatic hemangioma, if drug therapy fails. Pharmacologic treatment is used for symptomatic multiple liver hemangiomas. Embolization allows interim control of heart failure. A decreased mortality rate after interferon alfa-2a therapy is encouraging. (J Pediatr 1996;129:346-54)

Hemangioma and AVM are biologically different disorders; yet both exhibit "fast flow" and arteriovenous shunting. Thus both can be manifested as neonatal hepatomegaly, congestive heart failure, and anemia. [1] Liver hemangiomas eventually regress, just as they do in the skin, but complications result in a mortality rate of 30 percent to 80 percent. [2,3] AVMs never regress and have a higher, but not well-documented, Table 2 mortality rate. [1] Proper diagnosis once required either liver biopsy [4,5] or angiography [6-8]; these procedures have been superseded by ultrasonography and magnetic resonance imaging. [9,10]

Table 2. No caption available.

We analyzed 43 cases of infantile hepatic vascular anomalies treated at our institution during the past 27 years, focusing on (1) differential diagnosis of hemangioma versus AVM and (2) efficacy of treatment, using mortality rate as an end point.

METHODS

We reviewed the records of all infants with hepatic vascular anomalies seen at Boston Children's Hospital from January 1968 through December 1995 (n = 43). During the period from 1968 to 1984, diagnosis was made by clinical examination, angiography, surgical exploration, histologic examination, or autopsy. During the last decade, diagnostic evaluation has become noninvasive: ultrasonography, computed tomography, MRI, or a combination of these modalities. Biopsy was necessary for diagnosis in only two cases during the past 10 years.

Until 5 years ago, diagnostic confusion often resulted in the same therapy for both hemangioma and AVM. Radiotherapy or resection was the only treatment before

1968; operative therapy continued into the study period. Oral corticosteroid therapy for hemangiomas was first employed in our institution in 1968; embolization has been used selectively since 1985; and a trial of interferon alfa-2a began in 1990.

Response to therapy for hemangioma was documented by either serial ultrasonography
or MRI, with assessment for diminished size of lesion(s) and decreased blood flow in the hepatic vasculature. Treatment success was defined as survival of the child.

RESULTS

Arteriovenous malformation

Presentation. Only 4 (10 percent) of 41 infants, all female, had hepatic AVM. Three infants had congestive heart failure, hepatomegaly, and anemia at birth, and one had hydrops fetalis 3 weeks before delivery. The fourth infant manifested congestive heart failure, hepatomegaly, and anemia at 1 month of age in association with portal hypertension and gastrointestinal bleeding.

Diagnosis. Diagnosis of hepatic AVM was made by ultrasonography in three of four infants. It showed an increased number of enlarged vessels in the left lobe (n = 2) Figure 1(A) and in the right lobe and medial segment of the left lobe (n = 1). The proximal aorta, celiac axis, and hepatic artery were enlarged in all infants. In two patients the main portal vein and left hepatic vein were also dilated Figure 1(B). Two infants were studied with Doppler ultrasonography. In one infant, high-velocity arterialized portal flow was noted, indicating arterioportal shunting.

Figure 1. Hepatic AVM, present at birth (Table 1, patient 4). A, Longitudinal sonogram showing multiple tubular anechoic structures in left hepatic lobe (arrows). B, Transverse sonogram of liver, demonstrating enlarged left hepatic vein draining the vascular malformation (arrowheads).

Table 1. Treatment of hepatic vascular anomalies in infancy (1968-1995)

The diagnosis of AVM was confirmed by angiography and histologic examination in all four infants. In one infant, angiography was done post mortem. In four of four AVMs, angiography demonstrated a focal collection of abnormal vessels and arteriovenous shunting, without parenchymal blush. Arterioportal shunting was confirmed in one infant. MRI in one infant with AVM showed a localized vascular anomaly with increased signal intensity on T1-weighted images and numerous large "flow voids."

Liver function test results were normal in all infants. One infant with AVM had hyperbilirubinemia at 1 month of age.

Treatment. Three of four infants with AVM underwent coil embolization to branches of the hepatic artery and had subsequent hepatic lobectomy. One of these infants received inappropriate corticosteroid therapy for 3 weeks before resection.

Mortality rate. The mortality rate for hepatic AVM was 50 percent (2/4). One death occurred immediately after birth, before therapy, and postmortem angiography and autopsy revealed multiple AVMs involving both hepatic lobes and bilateral pulmonary hypoplasia. The other infant died of uncontrollable intraoperative hemorrhage after hepatic embolization and small bowel resection.

Follow-up evaluation. One child was alive and well, without evidence of AVM, 9 years after embolization and hepatic lobectomy. The other living child had a recurrent vascular hepatic mass, 1 year after partial resection, that evidences focal signal abnormalities with vascular flow voids on MRI. Angiography demonstrated multiple small arteries and early venous filling; however, the precise nature of this "recurrent" high-flow vascular anomaly remains uncertain.

Hemangiomas. Ninety percent of hepatic vascular anomalies were hemangiomas (n = 39). The gender ratio was 23 girls to 16 boys. The mean age at presentation was 2 weeks (range, birth to 6 months of age).

Presentation

Solitary tumors. Sixteen infants had a single hepatic hemangioma. Small hepatic hemangiomas were found unexpectedly in four infants who had imaging studies for other medical conditions; one of these infants also had four small cerebral hemangiomas. Hepatomegaly alone, or in association with jaundice, was the only sign of hepatic hemangioma in 11 infants; all but two of these had a solitary lesion. Of 16 children with a single large hemangioma (all involving the entire left lobe), three had hepatomegaly, congestive heart failure, and anemia as presenting symptoms at birth but had no cutaneous tumors.

Multiple tumors. Of 23 infants with multiple hepatic hemangiomas, 19 (83 percent) manifested the triad of hepatomegaly, congestive heart failure, and anemia between 1 and 16 weeks of age. Of the 23 infants, 17 also had multiple cutaneous hemangiomas, defined as more than five skin lesions apparent before 2 weeks of age. Of the 17 infants with cutaneohepatic tumors, 13 (76 percent) had congestive heart failure. No infant with either single or multiple lesions had portal hypertension subsequently.

Diagnosis

Biochemical and hematologic parameters. Abnormal results of hepatic chemistry studies (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase) were found in 6 of 37 infants; five of these six infants had multiple liver hemangiomas. Congenital hyperbilirubinemia was noted in three infants with single hepatic hemangioma. Hyperbilirubinemia occurred later (between 5 days and 3 weeks of age) in four infants, all but one of whom had multiple hepatic hemangiomas. Lactic dehydrogenase activity was elevated in six cases; three of the patients had a single hepatic tumor. Five infants had low-grade thrombocytopenia, not designated Kasabach-Merritt phenomenon.

Radiologic studies. Of 39 infants, 32 had either solitary or multiple nodules visualized by ultrasonography. These tumors were either inhomogeneous in echogenicity (i.e., hypoechoic, isoechoic, and hyperechoic) or predominantly hypoechoic, in comparison with hepatic parenchyma. Four of six solitary lesions had calcifications Figure 2(A). The proximal segment of the aorta, celiac trunk, hepatic artery, superior mesenteric artery, or hepatic veins, or a combination of these, were enlarged in 19 infants with congestive heart failure Figure 2(B). Doppler ultrasonographic examination (n = 27) demonstrated enlarged arteries and veins, both at the periphery and centrally within the mass. Spectral analysis

revealed increased arterial and venous flow velocity. In some cases, pulsatile venous flow was documented, indicative of arteriovenous shunting. Follow-up ultrasonographic studies, performed in infants undergoing pharmacologic therapy, demonstrated decreasing size of lesions, caliber of the nutritive arteries, and draining veins as well as diminishing flow within these vessels.

Figure 2. Solitary hepatic hemangioma, present at birth (Table 1, patient 12). A, Transverse sonogram of right hepatic lobe, showing well-circumscribed echogenic mass with multiple calcifications (arrow). B, Longitudinal sonogram of right hepatic lobe, showing enlarged veins at periphery of tumor (arrowheads).

By computed tomographic examination (n = 3), hemangiomas evidenced lower attenuation than did normal hepatic parenchyma on precontrast scanning and variable enhancement after administration of contrast medium. Two solitary lesions demonstrated calcification and inhomogeneous enhancement. Hemangiomas with greater flow typically had aortic dilation and enlarged hepatic vessels.

MRI studies (n = 9) demonstrated characteristic discrete areas of signal abnormality (decreased signal compared with normal hepatic parenchyma on T1-weighted images and increased signal on T2-weighted images) associated with flow-voids and uniform contrast enhancement Figure 3. In addition, dilation of the hepatic veins, celiac vessels, and suprahepatic aorta was seen in infants with congestive heart failure. Two infants with solitary tumors had equivocal MRI findings that could not be differentiated from those of hepatoblastoma. Serial MRI studies, used to monitor drug therapy, demonstrated progressively decreasing size of hemangiomas with diminishing caliber of adjacent hepatic veins and arteries.

Figure 3. Serial MRI examination of 4-month-old child with multiple hepatic hemangioma (Table 1, patient 23). Axial T2- weighted image shows hepatomegaly with multiple well-circumscribed and hyperintense nodules in both hepatic lobes. Large flow-voids (arrows) represent enlarged fast-flow, hepatic vessels.

Fifteen infants with hepatic hemangioma underwent angiography. The typical pattern was dilation of the hepatic arteries and veins with dense parenchymal staining, with (n = 10) or without (n = 5) arteriovenous shunting. Seven infants had extensive collateral supply from adjacent intercostal arteries, superior mesenteric artery, and renal-adrenal arteries. The angiographic distinction between hemangioma and AVM was difficult in two cases. The portal circulation was studied in one infant, who had multiple large direct fistulas between the portal and hepatic veins.

Treatment. Treatment of hepatic hemangiomas evolved with time: surgical resection or corticosteroid (after 1968), embolization (after 1985), and interferon alfa-2a (after 1990). Five children with small asymptomatic liver hemangiomas (single or multiple) were not treated. Results of the various therapies are documented in Table 1.

Surgical resection Table 1. Surgical resection (standard hepatic lobectomy or extended lobectomy) was undertaken (mean age, 2 1/2 weeks) in 10 infants with solitary hemangioma. One infant underwent embolization preoperatively, as noted in Table 1. Two infants underwent resection because of a suspected diagnosis of hepatoblastoma.

Embolization. Steel wire or platinum coils [7] and polyvinyl alcohol foam particles [1] were used to occlude hepatic arteries and collateral vessels in seven infants. In six infants, corticosteroid therapy failed; all but one had congestive heart failure. Two infants demonstrated sufficient improvement after embolization to permit extubation. Hypertension secondary to diminished metabolism of endogenous aldosterone and catecholamine by the liver also resolved after embolization in one of these two infants. Embolization was marginally effective in two of six cases because of multiple collateral vessels. [11]

Corticosteroids Table 1. Twenty-two infants with symptomatic liver hemangiomas were given orally administered corticosteroids, prednisone or prednisolone, 2 mg/kg per day. Therapy was initiated at birth to 9 months of age; average duration of drug therapy was 6 weeks. Accelerated regression was observed in only 5 of 22 corticosteroid-treated infants (23 percent success rate). One infant was lost to follow-up evaluation after age 6 months. After 1990, infants unresponsive to corticosteroid therapy were subsequently treated with interferon alfa-2a (n = 12).

Interferon alfa-2a Table 1. Six infants were in congestive heart failure before treatment. Six infants had massive hepatomegaly with multiple lesions involving both lobes Figure 3. Another infant had a single large hepatic hemangioma. At a mean age of 8 weeks, 12 of 13 infants received interferon alfa-2a after failure of corticosteroids and 1 after failure of both corticosteroids and embolization. The average duration of interferon alfa-2a treatment was 7.8 months (range, 24 days to 14 months). Accelerated regression was observed in 11 of 13 interferon-treated
infants (85 percent success rate).

Mortality rate. The combined mortality rate for 39 treated and untreated infants with hepatic hemangioma was 18 percent (7/39). Mortality rates differed for the various therapies in the 33 treated infants Table 1. One infant died before treatment.

Surgical resection for solitary hepatic hemangioma had a mortality rate of 20 percent (2/10). Both of the infants who died had thrombocytopenia, and death occurred because of uncontrollable intraoperative bleeding.

The mortality rate for embolization was 43 percent (3/7). All but one infant had been initially treated with corticosteroids. Two infants died of uncontrolled intraperitoneal bleeding and one of sepsis caused by small bowel infarction, after embolization.

Corticosteroid therapy had a mortality rate of at least 30 percent (3/10). One infant died of congestive heart failure and two died after embolization. Treatment with interferon alfa-2a had a mortality rate of 15 percent (2/13). One death occurred after 24 days of interferon therapy that began at 7 months of age; autopsy was not done, and the cause of death is unknown. The other death was from respiratory, renal, and hepatic failure. This child's course was remarkable in several respects. She was first noted to have hepatomegaly during the first weeks of life. Radiographic examination demonstrated multiple hepatic hemangiomas. The massively enlarged liver began to impinge on her lungs and renal vasculature, necessitating mechanical ventilation. Treatment with corticosteroids failed, and interferon alfa-2a therapy was started. Consumptive coagulopathy and oliguria subsequently developed. Vincristine [12] was given, but the infant's condition remained critical. Subsequent MRI showed minimal

regression but unchanged hepatomegaly. Embolization was considered, but in the absence of congestive heart failure, high-dose irradiation was directed to the right hepatic lobe. The infant died despite these various therapies. Autopsy revealed a 1395 gm liver filled with hemangiomas; some lesions were involuting, but most striking were the veno-occlusive changes. The infant also had bilateral temporal lobe hemangiomas that bled and caused agonal seizures.

DISCUSSION

Ninety percent of hepatic vascular anomalies in this study were hemangiomas and 10 percent were arteriovenous malformations. Hepatic hemangiomas are typically multiple, involving both lobes, usually in association with numerous cutaneous hemangiomas [2,13-15] and sometimes with "hemangiomatosis," involving the central nervous system, respiratory system, and gastrointestinal tract. [15-17] We found that cutaneohepatic tumors were premonitory for heart failure and anemia between age 1 and 16 weeks. In contrast, infants with solitary hepatic hemangioma typically manifested congenital hepatomegaly, congestive heart failure, and anemia, the same triad as infants with hepatic AVM Figure 4.

Figure 4. Differential diagnosis of hepatic vascular anomalies in infancy. CHF, Congestive heart failure; AV, arteriovenous.

In the absence of cutaneous hemangiomas, radiologic studies are critical to differential diagnosis Figure 4. Unfortunately, the terms hemangioma and AVM have been confused or used interchangeably in the literature. [18,19]

Ultrasonography was used to distinguish AVM from hemangioma, document solitary versus multiple hepatic hemangiomas, and monitor therapy. MRI provided a better assessment of hemangiomatous extent and overall liver size, especially when the entire liver was involved. MRI was also used to demonstrate tumor regression during therapy. Although both MRI and angiographic findings were usually characteristic, sometimes they were indistinguishable from images of other vascular tumors or AVM. [20] One infant with a solitary tumor and equivocal MRI findings underwent lobectomy. In retrospect, this infant's tumor was fully grown at birth, and histopathologic examination confirmed that the tumor was involuting at the time of resection (at 9 days of age). Such rapid regression occurs in "congenital" hemangioma. [21] Angiographic study of adjacent collateral arteries and portal veins should be done before embolization or contemplated surgical resection.

Inappropriate inclusion of infantile hepatic AVMs could account, in part, for the high mortality rate in previously reported series of hepatic "hemangiomas." [1] The only effective therapy for hepatic AVM is embolization followed by hepatic lobectomy. The mortality rate was 50 percent in this small series.

Hepatic hemangiomas, like cutaneous tumors, invariably regress beginning late in infancy, [22] but unlike most cutaneous lesions, they are life-threatening during the proliferative phase. The mortality rate is 30 percent to 80 percent. [2,3] Before 1968, the only treatment was radiation, [23,24] proximal ligation of the hepatic arteries, [25-29] or surgical resection. [4,30,31] Radiotherapy carries a risk of other sequelae (e.g., cirrhosis, hepatosarcoma, and leukemia [32-34]) and should not be considered unless other therapies are contraindicated or unsuccessful. [9,24,35,36] Hepatic artery ligation is not always successful, and liver necrosis and abscess can occur. [35,37] We found surgical resection (lobectomy) to be effective therapy for isolated hepatic hemangioma; however, it

has the potential risks of uncontrollable bleeding, hepatic necrosis, and abscess, even in the absence of overt high-output congestive heart failure. [4,26]

Hepatic artery embolization can temporarily control life-threatening congestive heart failure. [11,38] The effectiveness of this technique is often limited by an extensive vascular supply from the portal veins and collateral arteries. [39,40] Furthermore, embolization can cause such complications as cirrhosis, sepsis, and hepatic infarction. [9,38,41,42] It should be reserved for infants with congestive heart failure severe enough to warrant intubation and pressor therapy and done in conjunction with pharmacologic therapy.

Not all infants with hepatic hemangiomatosis have congestive heart failure. [43] Five symptom-free infants were not treated in this series. Nevertheless, if hepatic hemangioma(s) involves an entire hepatic lobe or both lobes, pharmacologic
therapy probably should be started as soon as possible, even if the neonate is not in overt congestive heart failure.

Oral corticosteroid therapy has been used for hepatic hemangiomas for 25 years [15,44,45]; response rates range from 18 percent to 70 percent. [11,29,31,46,47] We found corticosteroid therapy to be effective in no more than 30 percent of infants. The corticosteroid mortality rate probably would have been higher if 12 unresponsive infants had not been treated subsequently with interferon.

We confirmed the effectiveness of interferon alfa-2a treatment for hepatic hemangiomas. [48-50] The mortality rate was 15 percent. Toxic effects included elevation in liver enzymes, neutropenia (at a low dosage), minor alopecia, and diminished appetite (at a high dosage). Spastic diplegia reversed in one infant and persisted in the other child, with continued improvement after successful completion of therapy. [51,52] Therefore we strongly advise careful neurologic and developmental assessment before and during interferon therapy.

Neonatal hepatic vascular anomalies are rare, the numbers in each group are small, and therefore recommendations for management cannot be rigid. On the basis of our experience, we advise combined embolization and resection for hepatic AVM. Pharmacologic therapy is indicated for symptomatic liver hemangiomas
and for either large or extensive multiple tumors in symptom-free infants. Embolization can be useful either for interim control of congestive heart failure (during pharmacologic therapy) or before resection of a solitary liver hemangioma that is unresponsive to drug therapy. If corticosteroid therapy fails, the drug dosage should be rapidly tapered and interferon alfa-2a therapy initiated. There is no evidence that the two drugs are synergistic; they may be countereffective. The relative efficacy of corticosteroids versus interferon alfa-2a should be evaluated by prospective interinstitutional study.

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