MRI Findings Common to Infantile Hemangiomas

Thesis submitted to the
University of Arizona College of Medicine - Phoenix
in partial fulfillment of the requirements for the degree of
Doctor of Medicine

Nirav Patel
Class of 2012

Mentors: Judith O'Haver, PhD, RN, CPNP; Harper Price, MD;
Richard Towbin, MD
Dedication

To my wonderful mentors Judith O’Haver, Richard Towbin, Ronald Hansen, and Harper Price.
Acknowledgements

I would like to thank the Dermatology and Radiology departments at Phoenix Children’s Hospital for all their contributions.
Abstract

Background: Infantile hemangiomas (IH) are the most common vascular tumors of infancy. Children may have Magnetic Resonance Imaging (MRI) to establish or confirm the diagnosis or to further evaluate lesions that do not improve with treatment.

Objective: Describe specific MRI findings common to infantile hemangiomas. Compare the imaging diagnosis with the clinical diagnosis of IH to determine diagnostic accuracy.

Methods: A descriptive retrospective chart review on a convenience sample. Twenty-six patients had a total of 31 MR studies in the group. From these 31 studies, 16 also had magnetic resonance angiography (MRA).

Results: Clinical diagnosis matched imaging diagnosis 96.8% of the time. Findings from imaging of the infantile hemangiomas included increased signal intensity on T2-weighted sequences (96.8%), isointense or decreased signal with T1-weighted sequences (83.9%) and
moderate to marked contrast enhancement (78.5%). Lesions appeared to be high flow (64.5%), demonstrated lobulation (58.1%), and displayed central, low signal intensity dots on T2-weighted sequences (54.8%). In contrast, cystic spaces, intraläsional DIC, phleboliths, focal intraläsional inhomogenities, septation, edema, fat stranding, aneurysms, venous ectasia, and shunts were not features regularly seen in imaging of IHs in this study.

**Limitations:** Small sample size on a convenience sample based at one institution.

**Conclusion:** There are specific features to infantile hemangiommas on MR imaging that can be used for aid in diagnosis.
Table of Contents

Introduction..................8
Materials and Methods.....14
Results........................19
Discussion.....................24
Conclusion.....................28
Future Directions...........29
References.....................30
List of Figures and Tables

Table 1- Features on MRI........15
Table 2- Features on MRA........16
Appendix 1.............................32
Introduction

Infantile hemangiomas (IHs) are the most common tumor of infancy. These benign vascular tumors affect 4-10% of infants (1-2). They are more common in females, are usually found on the head and neck, and have an increased prevalence in children born prematurely (3-5).

The differential diagnosis for vascular lesions in infants can include both vascular tumors and malformations and the continued use of outdated nomenclature can be confusing. In 1982, Mulliken and Glowacki attempted to clarify this by separating hemangiomas of infancy (classified as vascular tumors) and vascular malformations into two broad categories using histology, electron microscopy, and clinical findings. This classification is used by clinicians and has also been adopted by interventional radiologists (6).

Vascular malformations are congenital anomalies of vessels that may be differentiated by vessel type into capillary, lymphatic, venous, arterial, or combined lesions, such as aterio-venous malformation or veno-lymphatic malformation. Vascular malformations are differentiated from hemangiomas by their equal predominance in
males and females, normal endothelial cycle (no proliferative or involution phase), and proportionate growth with the child (6).

Hemangiomas of infancy are generally referred to as either infantile (present days to weeks after birth) or congenital and are classified according to the clinical depth of the lesion (superficial, deep or combined) and distribution (either segmental or focal). Generally, infantile lesions present with a precursor mark that may be seen at birth or the first few days to weeks of life followed by a “rapid growth phase” which may continue through 6-12 months of life. By one year of age most IH have reached maximum growth potential. Then lesions begin to involute over time entering the so called “involutional phase”, and the majority slowly resolves over the next 5-10 years (6-8).

Most infantile hemangiomas involute with little remaining skin change left to be seen, e.g., telangiectasias. However, in some cases the residual skin overlying the lesion maybe altered due to stretching from rapid growth or scar may have resulted from ulceration. The residual fibrofatty infiltrate that results during the involution phase may also not regress adequately with time. Thus the composition of the underlying skin may also be altered and replaced with loose, fibrofatty stroma. The impact of the physical alteration of the skin after
involution is dependent on the original size of the IH, the area of the body where the IH was located, and whether ulceration occurred. (8).

Many IHs require no treatment, as they will naturally involute with an acceptable appearance. However, treatment is indicated when ulceration is present, functional impairment occurs (e.g., obstruction of airway), pain develops, and there is risk for permanent disfigurement (e.g. nose, ears). This represents an estimated 10% of IHs (9-10).

Currently, there is a lack of evidence-based standards for treatment of hemangiomas that require intervention. Treatment options that have been studied include high dose systemic corticosteroids, vincristine sulfate, and interferon. All of these options pose risk due to systemic side-effects with the additional burden of close monitoring (1, 11-12).

In 2008, a case series of 11 children published in the *NEJM* by Leaute-Labreze et al., described the use of propranolol hydrochloride, a nonselective β-adrenergic blocking agent, as effective in arresting the growth and precipitating the rapid involution of extensive IHs (13). This report and the subsequent discussion and literature that have followed have changed the practice of many physicians treating infantile hemangiomas. Propranolol is now being used as treatment
for IHs due to the high efficacy and low side-effect profile (1). In many cases, it is considered first-line treatment.

A subset of patients with IHs also undergo imaging of their lesion. The reasons to order imaging vary. If the clinical diagnosis is in question, imaging may be done to obtain a support for a diagnosis. Some lesions are imaged to assess the extent of involvement, especially those around the orbits. Also, hemangiomas that fail to improve on treatment may be imaged to rule out another diagnosis that may mimic IH, such as a vascular malformation.

Imaging can be done using ultrasound, computed tomography (CT), and MR. Modalities such as plain radiograph and CT expose the child to radiation and are less effective at soft-tissue differentiation. High-resolution ultrasound does not expose the patient to radiation, but is very operator dependent. Therefore, MR is currently the modality of choice as it minimizes radiation exposure to the child and is able to analyze many facets of the lesion. MR provides the optimal way to characterize and diagnose the lesion and assess the vascular supply. MR is considered standard testing for syndromes with associated hemangiomas such as PHACE syndrome (posterior fossa malformations of the brain, large facial hemangiomas, arterial
anomalies, cardiac anomalies and aortic coarctation, and eye abnormalities) or PELVIS syndrome (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) (15-16).

To date, there have been few reports regarding the specific MRI/MRA features of just infantile hemangiomas (17-20). The findings are often reported along with other soft tissue vascular tumors and malformations such as arterio-venous malformations and include a small number of hemangiomas a part of larger study with patients of a wide age range (19-20), which makes comparison to other studies difficult.

The purpose of this study is to further describe specific MR findings of clinically diagnosed infantile hemangiomas as well as to compare the imaging diagnosis with the clinical diagnosis to determine diagnostic accuracy. Specifically we hypothesize that on MR examination the majority of IHs would be seen as lobulated and enhancing lesions with T2 hyper-intensity and high flow. We would not expect to see cystic spaces or phleboliths, as these should be common to vascular malformations.
The results of this study will aid both clinicians and radiologists to properly identify a suspected lesion as an infantile hemangioma on MRI.
Materials/Methods

Design: A descriptive retrospective chart review on a convenience sample.

Sample: All infants who received propranolol for the treatment of an infantile hemangioma in the pediatric dermatology clinic at Phoenix Children’s Hospital from January 1, 2008 to March 2011 that received MRI or/and MRA imaging. This sample is a subset of patients from a primary study entitled, “Infantile Hemangiomas Treated with Propranolol, Description of the Phoenix Children’s Hospital Experience.”

Inclusion Criteria: 1) Clinically diagnosed IH(s); 2) Propranolol administered for treatment of the IH; 3) Magnetic resonance (MR) imaging conducted on IH.

Exclusion Criteria: No specific exclusion criteria

Instruments used for data collection: A data collection sheet (Appendix 1) containing all variables (Table 1 and 2). Possible variables for a vascular lesion, and, more specifically, an infantile hemangioma were established for this study by review of the literature, and also through the expert opinion of Dr. Richard Towbin (21).
### Table 1

<table>
<thead>
<tr>
<th>Variables Recorded on MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Clinical and imaging diagnosis</td>
</tr>
<tr>
<td>- Volume of lesion</td>
</tr>
<tr>
<td>- Features of cystic spaces seen on MRI</td>
</tr>
<tr>
<td>- Pre and post-contrast appearance</td>
</tr>
<tr>
<td>- Usage of additional therapy beyond propranolol presence of intralesional DIC</td>
</tr>
<tr>
<td>- Presence of phleboliths</td>
</tr>
<tr>
<td>- Presence of high or low flow in the lesion</td>
</tr>
<tr>
<td>- Presence or absence of flow voids</td>
</tr>
<tr>
<td>- Presence of lobulation</td>
</tr>
<tr>
<td>- Presence of septation</td>
</tr>
<tr>
<td>- Presence of central low signal intensity dots on T2 weighted images</td>
</tr>
<tr>
<td>- Level of T1 or T2 intensity</td>
</tr>
<tr>
<td>- Presence of focal inhomogenities</td>
</tr>
<tr>
<td>- Presence of edema</td>
</tr>
<tr>
<td>- Presence of fat stranding</td>
</tr>
<tr>
<td>- Location of the lesion.</td>
</tr>
</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th>Variables Recorded on MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Presence of capillary blush</td>
</tr>
<tr>
<td>- Aneurysms</td>
</tr>
<tr>
<td>- Venous ectasia</td>
</tr>
<tr>
<td>- Vessel size</td>
</tr>
<tr>
<td>- Shunts</td>
</tr>
<tr>
<td>- Feeding artery</td>
</tr>
</tbody>
</table>
Data was entered and analyzed using IBM SPSS Statistics Professional 20.0.

*Method:* Approval for this study was obtained through Phoenix Children’s Hospital Institutional Review Board. Clinical records and CPT codes of 228.00/228.1 (hemangioma of unspecified site or skin) identifying all patients seen in the dermatology clinic at Phoenix Children’s Hospital with the diagnosis of hemangioma (year 2008 to March 2011) were used for patient selections. Charts were then reviewed and all patients who were treated with propranolol were identified. Of the approximately 750 children with the diagnosis of hemangioma identified, there were approximately 170 children treated with propranolol. Analysis revealed that 26 patients met the inclusion criteria for a total of 31 MR studies in the group. From these 31 studies, 16 also had MRA.

A single radiologist with expertise in vascular lesions analyzed each radiologic study. The radiologist recorded the presence or absence of variables seen in each study on the data sheet along with the age of the patient, volume, and reason for MR. (17-21).
Analysis of data: A power analysis was not required as this is a
descriptive study of a convenience sample. Frequencies of each variable
were determined. One-way ANOVA was used to investigate the
relationship between age & volume. The remainder of the variables
were categorical variables and were analyzed using Spearman rho. A
Fisher’s exact test was used to determine the relationship between
feeding artery and location (p=.02).
Results

Retrospective analysis revealed that 26 patients met the inclusion criteria for a total of 31 MR studies in the group from January 1, 2008 to March 2011. From these 31 studies, 16 patients also had MRA. The age range in our group at the time of MR was 29 days to 1260 days (mean, 345 days, SD=345 days). Of the 26 patients, 22 were female and 4 were male. Full-term infants represented 73.1% of our group. The volume of lesions imaged ranged from 2.61mm³ to 1,562,992mm³ (mean=154,594 mm³, SD=339,558mm³). Significant interactions were found between volume by intensity, volume by location, age by features, age by DIC, and age by phleboliths using one-way ANOVA.

Reason for MR

Of the 31 studies in the group, 28 (90.3%) were ordered to assess extent of involvement, while 3 studies were ordered due to lack of clinical improvement (9.7%). Five patients had repeat MRs to assess extent of the lesion or lack of improvement. Except for a change in volume (almost all decreased), there were no other notable changes of statistical significance between the repeat studies.
**Diagnostic and Clinical Correlation**

Prior to imaging the clinical diagnosis was an IH in 100% of cases (n=31). The radiological diagnosis post imaging was IH for 97% (n=30) of the sample. The radiologic diagnosis for one study was an arterio-venous malformation (AVM).

The AVM that was identified by MR differed from the IHs both on imaging. The AVM demonstrated microcystic spaces and intralesional DIC, two features not found on any of the radiologically confirmed IHs in our study. Additionally, the lesion lacked flow voids, was considered to be low flow, had hyperintensity on T1, and lacked low signal intensity dots on T2.

**Characteristics of Contrast Enhancement**

Analysis of contrast enhancement revealed that 9.7% of IHs showed no enhancement, 9.7% showed mild enhancement, 32.3% showed moderate enhancement, and 45.2% showed marked enhancement.
**Characteristics on T1-Weighted Images**

T1-weighted images demonstrated iso or decreased signal on 83.9% of IHs, hyperintense signal on 9.7%, and heterogenous signal in 6.5%.

**Characteristics of T2-Weighted Images**

Central low signal intensity dots on T2-weighted images were seen in 54.8% on IHs. T2-weighted images demonstrated hyperintense signal on 96.8% of IHs. One IH showed isointense signal. Central low signal intensity dots on T2-weighted images were seen in 54.8% on IHs.

**Flow and Structural Characteristics**

High flow IH lesions represented 64.5% while 35.5% were low flow. Flow voids, which correspond with high flow, were seen on 64.5% of IHs. Additionally, 58.1% exhibited lobulation while only 12.1% had septation. Focal inhomogeneities were seen in 16.7% of IH.
**Angiographic Characteristics and Location**

Of the 15 patients in our group that had MRA, no lesions demonstrated aneurysms, venous ectasia, or presence of a shunt. Capillary blush was seen in 6.7% of IHs.

A predominant feeding artery was identified in 45.2% of IHs through MRA or MR. Of the predominant feeding arteries identified, the facial artery was seen in 29% of IHs, the superficial temporal in 3.2%, the ophthalmic in 6.5%, and the circumflex humoral in 6.5%. No definitive feeding artery was detectable in 54.8% of lesions. The mean vessel size was 3.3mm.

The most common location for imaged IHs was the orbit (25.8%). Also, the relationship between location and which feeding artery supplied the hemangioma was found to be statistically significant using Fisher’s exact test (p=.022). This was most strongly seen in parotid lesions. In all parotid lesions in which a feeding artery could be detected, the facial artery was found to be the major feeding artery. For all other locations, it was difficult to identify a dominant artery. This may be in part due to the fact that many of the patients did not have MRA.
*Features Not Seen on MR*

Intralesional DIC, microcystic spaces, edema, or fat stranding was not identified in any lesions radiologically diagnosed as an infantile hemangioma. A single lesion diagnosed as an IH had phleboliths, however other features of the lesion were consistent with findings found in other IHs in our study. Additionally, a second lesion also had phleboliths, but was diagnosed as an AVM.
Discussion

This study demonstrates that a radiologic diagnosis of IH appears to be highly accurate when compared to the clinical diagnosis (at our institution). Accuracy in this case is defined as the imaging diagnosis matching the clinical diagnosis. Our study had 96.8% accuracy. Imaging was largely ordered to assess extent of involvement and determine if a lesion was truly an IH. It appears that MR is useful in confirming the diagnosis of IH in cases of high clinical suspicion.

There appears to be characteristic radiologic findings of IHs. They demonstrate moderate to severe contrast enhancement, lobulation, iso or decreased signal intensity with T1-weighted imaging, hyperintense signal on T2-weight imaging, central, low signal intensity dots on T2-weighted images, and appear to be high flow.

Cystic spaces, intrallesional DIC, phleboliths, focal inhomegenities, septation, edema, fat stranding, aneurysms, venous ectasia, and shunts were not features regularly seen on IHs in this study and are more likely to be seen with other types of soft-tissue vascular tumors or malformations. This was evident when looking at the starkly contrasting characteristics of the sole AVM found in our sample. Although our study only offers one example, it appears that
separating an IH from vascular malformations is possible and can be done according to specified characteristics and criteria. This is helpful as some IHs cannot be diagnosed with 100% confidence clinically and would otherwise require a biopsy to determine final diagnosis.

This study reports on the largest sample with the greatest amount of radiologic variables analyzed for IH. Previously, similar reports involved smaller sample sizes and used hemangioma as a generic term to represent all hemangiomatous lesions and vascular malformations. Additionally, these reports included results that contained MR data of soft-tissue masses and hemangiomas found in patients of broader age ranges with fewer criteria included. When looking at infantile hemangiomas in older children, such as those that have involuted, the characteristics on imaging may differ (17-20).

Our study was able confirm findings seen in other studies such as lobulation being more common in IHs along with iso or decreased signal with T1-weighted imaging and hyperintense signal on T2-weight imaging (17-20).

Septation was a feature not regularly found in our group. This differed from the report by Teo et al. in 2000 that reported a large percentage of “hemangiomatous” lesions with septation. Additionally,
we did not see the presence of central, low signal intensity dots to as large of a degree as reported by Teo et al. It is possible that the differences in this finding could be due to the manner in which the sample was described. Teo and his colleagues grouped all hemangiomatous lesions and vascular malformations together as their sample. Our sample was limited to the clinical diagnosis of infantile hemangiomas only (20).

The presence of central, low signal intensity dots have been postulated to possibly represent smooth muscle components, fast flow, calcifications, or fibrofatty septa (20, 22). Based on the characteristics of the hemangiomas in our study, we believe that these dots represent fibrofatty septa. Almost all hemangiomas in our study were high flow and likely had smooth muscle components, but not all lesions had fibrofatty septa as some lesions were likely in regression and some were still evaluated while in a growth phase. Only the lesions in regression would have been expected to exhibit fibrofatty septa. This could explain the finding that only 54.8% of IHs had these dots in our study.
Similar to the study reported by Kaplan et al., which imaged 11 patients with soft-tissue and mucocutaneous hemangiomas, we found that phleboliths were rarely visible on IHs (19).

Our study did have some limitations. Part of the radiologic accuracy could be related to the fact that the radiologist who examined each hemangioma works in this facility and reviews a large number of vascular lesions in children and therefore is very familiar with the characteristics of these lesions. As this expertise may be unique we propose our findings can aid in diagnosing IHs in centers with less volume and experience. A second limitation is our small sample size. Although we did have a larger number of hemangiomas when compared to other studies, our sample size was still relatively small to make more significant comparisons. A larger sample size would have aided in gathering additional data such as the common feeding artery for each location. A third limitation is that our data is based on the subjective analysis of one radiologist. Having multiple radiologists reading each study would have provided confirmatory data and established inter-rater reliability among providers.
Conclusion

The results of this study suggest radiologic criteria that may be helpful to radiologists who are evaluating vascular lesions believed to be IH. We propose the findings in this study can be used by radiologists as possible inclusion and exclusion criteria for diagnosis of IH with MR imaging when there is a high index of suspicion, as we believe these combination of findings has predictive value and may be confirmatory to avoid additional testing on susceptible lesions.
Future Directions

In future studies, it would be of benefit to have a larger number of patients and imaging studies. Future studies would also be more meaningful if more than one radiologist evaluated each study. This would allow for determination of inter-rater reliability, as well and the general acceptance of our variables by radiologist could be studied.

Validating the findings of this study should also be done in a blind manner. One way to do this would be to supply a radiologist with the MR images of the patient without diagnosis and allow him or her to reach a diagnosis using the characteristics found in this study. These findings could then be compared against a gold standard such as biopsy or clinical observation until resolution of the IH.

Finally, looking at serial imaging of patients on propranolol over time during both the rapid growth phase and the involution phase may better define the radiologic natural history of IHs. This would be difficult to justify and accomplish in the pediatric population as the usage of MR requires anesthesia and multiple studies would likely be required to see any changes.
References


<table>
<thead>
<tr>
<th>Study #</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings</th>
<th>Clinical Diagnosis (ICD 9 code):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis on imaging (ICD 9 code):

Volume: ellipsoid = \( \frac{4}{3} \pi r_1 r_2 r_3 \)

Features of cystic spaces: None 0  Microcysts 1  Macrocysts 2  Mixed 3

Pre and post contrast appearance: No enhancement 0  Mild 1  Moderate 2  Severe 3

Why was MRI ordered? PHACES/PELVIS 0  No improvement 1  Assess degree of involvement 2

Functionally threatening 3

Presence of intralesional DIC: yes 1  no 0

Presence Phleboliths: yes 1  no 0

Type of flow: High 1  Low 0

Presence or absence of flow voids: yes 1  no 0

Presence of lobulation (considered lobulated if there is internal septation): yes 1  no 0

Presence of septation (considered septate if septae were divided into smaller compartments): yes 1  no 0

Presence of central low signal intensity dots on T2 weighted images (present if three or more low intensity punctate dots were seen in the center of the lesion): yes 1  no 0

Level of T1 or T2 intensity (isosignal, hypersignal, heterogenous): isosignal 0  hypersignal 1  heterogenous 2

Focal inhomogenities: yes 1  no 0

Edema: yes 1  no 0

Fat stranding: yes 1  no 0

If angiography, description: presence of capillary blush: yes 1  no 0  ; aneurysms: yes 1  no 0  ; venous ectasias: yes 1  no 0  ; shunts: yes 1  no 0  ; vessel size:  ; Which feeding artery:

Facial 3  Superficial Temporal 4  Ophthalmic 5  Maxillary 6

Additional Findings (free text):