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ORIGINAL ARTICLE

Imaging studies in pediatric fibromuscular dysplasia (FMD): a single-center experience

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Abstract

Background Fibromuscular dysplasia (FMD) is a non-inflammatory vascular disease that in children unlike in adults shows no sex predilection. FMD is often underdiagnosed, and its pathophysiology is unclear. Delayed diagnosis may lead to refractory hypertension and decreases the chance of successful treatment. Doppler ultrasound (US), magnetic resonance angiography (MRA), computed tomography angiography (CTA), and catheter-based angiography (angiography) are currently used to help make a clinicoradiological diagnosis of FMD. The main aim of the study was to compare the efficacy of imaging modalities which can allow for earlier and improved detection. Furthermore, an anatomical mapping of the location of lesions can help determine the best treatment modalities.

Methods All patients with non-syndromic non-inflammatory renovascular hypertension were recruited from the Nephrology Department at the Children's Hospital of Philadelphia (CHOP) and enrolled in the U.S. FMD Registry maintained at the University of Michigan. Clinical presentation and imaging findings on US, CT, and MRI of children diagnosed with FMD were evaluated.

Results Mean age at diagnosis was 7 ± 4.9 years (4 months–17 years). Family history of hypertension (HTN) (52%), FMD (8.7%), Caucasian (60%), headache (48%), and HTN (80%) were the most prevalent symptom and sign at presentation. Bruits were 100% specific for renal artery stenosis (RAS) diagnosis but were heard in the minority of patients (3 patients, 12%). FMD was mainly unifocal within a single site (68%) or multiple sites (28%) and involved the main or first order renal branch in about 68% of children. Isolated distal lesions beyond the second order branches were found in about 25% of children. US imaging was significantly less sensitive than angiography (28%, $p = 0.003$). MRA had a better sensitivity (62.5%, $p = 0.3$) than US. Overall, CTA had the best sensitivity (84.2%, $p = 0.4$) compared to angiography; however, only angiography showed distal vessel disease.

Conclusions Limitations of the study include the sample size and biases—only patients diagnosed with FMD were included in this study and most patients were referred to a pediatric nephrologist for unexplained hypertension. Angiography should be performed as part of the initial work-up of any child suspected of having renovascular FMD, regardless of the findings seen on US, MRA, or CTA.

Keywords Angiography · Fibromuscular dysplasia · Hypertension

Introduction

Renovascular disease is responsible for approximately 5–25% of hypertension in children [1–5]. Fibromuscular dysplasia (FMD) is the most common cause of renal artery stenosis (RAS) in children [3]. Fibromuscular dysplasia is associated with arterial vascular stenosis, arterial aneurysms, and dissection of affected arteries [6–8]. The prevalence of FMD in children is presently unknown, and although originally thought to be a rare disease, this notion has recently been challenged by novel research emerging from patient registries in North America and Europe [7–9]. The disease is often overlooked and underdiagnosed given it may be asymptomatic and primarily limited to silent hypertension [1, 6, 9]. Delayed diagnosis may lead to refractory hypertension and decreases the chances of successful treatment [6, 9]. Elucidation of factors that can assist in diagnosis and a comparison of the efficacy of imaging modalities may allow for earlier and improved detection.

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Furthermore, anatomical mapping of the location of lesions can help determine the best treatment modalities.

Fibromuscular dysplasia can present with various vascular involvement with the multifocal variant, characterized by arterial segments of variable length and alternating diameters (string-of-beads), being most prevalent in adults [8, 9]. However, FMD can also be unifocal; unifocal disease can occur in a single artery or in multiple arteries and can be of variable length [8, 9]. In children, the stenosis is often tubular. More recently, arterial tortuosity marked by the appearances of an S-curvature in the internal carotid and coronary artery dissection in young women has been associated with FMD [8]. Fibromuscular dysplasia is reported to be more common in women [6, 10] whereas men with FMD have been shown to be more susceptible to dissections and aneurysms [10]. However, children with FMD seem less likely to have aneurysms and dissections, and the gender gap is much less prominent with roughly a 3:2 ratio of girls to boys being diagnosed compared to 47:3 ratio of females to men [11]. Children are also more likely to have hypertension at diagnosis than adults [11]. Of note, FMD in children is most prevalent in the renal arterial bed, but is by no means isolated to them and can affect any major vascular bed in the body [10]. Depending on the vascular bed involved, patients will show different clinical manifestations [6, 11].

Presently, the most common way to make a presumptive diagnosis of FMD is through radiological imaging. Imaging includes Doppler ultrasound (US), magnetic resonance angiography (MRA), computed tomography angiography (CTA), and the gold standard, catheter -based angiography (angiography) [6]. Ultrasound generates images based on short ultrasound pulse waves; it is specific but is also the least sensitive modality and is highly dependent on radiologist and technical experience [6].Ultrasouond is useful to show kidney size discrepancy and blood flow velocity, but is compromised by respiratory motion [6]. Magnetic resonance angiography uses magnetic fields to produce images that can indicate renal size, flow, and main renal artery stenosis. Magnetic resonance angiography offers less spatial resolution than CTA but eliminates radiation exposure [1, 6]. Three-dimensional CTA can indicate renal size, wall thinning, but requires the use of injected contrast materials along with X-ray imaging. Unlike MRA, CTA is not compromised by respiratory-related movement [1, 11–13]. Angiography provides the most spatial resolution but is also the most invasive as it involves a percutaneous catheter being inserted into an artery [6].

The aim of this study was to evaluate the clinical and radiological outcomes of children diagnosed with presumptive renovascular FMD seen at a single pediatric center.

We conducted a cross sectional study on patients with renovascular hypertension. Patients were recruited from the Nephrology Department at the Children's Hospital of Philadelphia (CHOP). Since the histopathology of FMD is rarely available, diagnosis was based on radiological findings [6]. Fibromuscular dysplasia was considered when hypertension was not due to a defined secondary and/or genetic cause, when severe hypertension was present in young children, when multiple drugs were needed to control the blood pressure (BP), when there was an abdominal bruit, and when imaging studies suggested the presence of RAS. Patient-related information was obtained from the electronic medical record (EMR), and data forms were completed to enroll the patient into the U.S. FMD Registry. This national de-identified data registry is maintained at the University of Michigan.

Information collected included demographics, family history, medications, symptoms, signs, diagnostic test results, and therapeutic procedures. Subsequent data forms were completed with each follow-up and added to the patient's file in the national FMD database. All patients were assigned an ID number, and the data forms were stripped of identifying information. Only patients diagnosed with renal FMD at CHOP were included in this study. Children's Hospital of Philadelphia electronic medical records were used to supplement the registry data on diagnostic imaging. These electronic records included information on the specific sites of lesions, the severity of the lesion, and any complications that arose from the imaging techniques. A total of 26 pediatric patients with FMD involving the renovascular bed were seen at CHOP. However, only 25 patients were considered for analysis as one patient did not have angiography.

Statistics

Summary statistics are presented as proportions, means, ranges, and standard deviations. Statistical significance was determined by using Fisher's exact test, where applicable. These statistical functions were carried out using RStudio. Blood pressure percentiles and *z*-scores were determined using the guidelines stated in "The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents" [14].

Imaging modality findings were evaluated using sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) [15]. Each kidney was looked at individually. Due to inclusion bias (only patients with FMD considered), specificity, sensitivity, and predictive values were estimated using the following process: If an imaging technique—CTA, MRA, US—showed evidence of FMD in a kidney and angiography supported the diagnosis of FMD, then the result was considered a true positive. If an imaging technique showed no evidence of FMD in a kidney and the angiography also showed no evidence, the result was considered a true negative. If the imaging technique showed no evidence of FMD in a renal artery but angiography did, then the result was considered a false negative. If the imaging technique showed no evidence of FMD in a kidney but angiography did, then the result was considered a false negative.

Results

Patient demographics, symptoms, and signs

The demographics, symptoms, and signs of the patients are presented in Table 1. Of the 25 patients included in the study, the mean age at diagnosis was 7 ± 4.9 years (range from 4 months to 17 years). The majority of children were Caucasian (60%, $n = 15$ patients) and female (52%, $n = 13$ patients). There was no single symptom found to be present in the majority; however, headaches were documented in 48% of patients (12 patients), 80% (20 patients) had a documented history of hypertension, and the other 20% (5 patients) were diagnosed with hypertension at presentation to our center. Only 12% of children (3 patients) had a renal bruit at diagnosis. In our study, there were no symptoms of neck pain, tinnitus or pulsatile tinnitus, and amaurosis fugax and no signs of stroke, hemispheric transient ischemic attack (TIA), or myocardial infarction (MI).

Patient initial blood pressures

Baseline BP values are shown in Table 2. The average systolic blood pressure among our study population at the diagnosis was 130.4 ± 27.5 mmHg (range 102–228 mmHg). The average diastolic blood pressure was 73.56 mmHg ± 17.8 (range from 48 to 120 mmHg). On average, the systolic and diastolic blood pressure percentiles were 89.8% ± 19.4% (46.7–100%) and 74.5% ± 25.7% (range 10.6–99%) respectively. All patients were hypertensive at diagnosis with some having a documented history of hypertension and others being diagnosed with hypertension during baseline visit. Forty percent of the patients were on no anti-hypertensive drugs at enrollment (at initial presentation to CHOP), 28% were on one drug, 20% on two, 8% on three, and 4% on four.

Family history

A known family history of FMD was present in 8.7% of patients (2 patients). There was no family history of stroke, dissection, or Ehlers–Danlos syndrome in any of the patients. All other documented family history—sudden death, aneurysm, hyperlipidemia, and kidney stones—were only found in one patient. Two of the patients in the study were adopted and did not have documented family histories.

Imaging of renal arteries

The results of each imaging modality are summarized in Table 3. Angiography was used as the gold standard for comparison. All images were reviewed by the Chief of Interventional Radiology and were not blinded. US imaging was significantly less sensitive (28% US vs. 100% angiography, $p = 0.003$) at picking up lesions in the renal vasculature and was the least sensitive imaging technique. Notably, US sensitivity rises to 38.5% ($p = 0.08$) if only main renal artery lesions are considered. The NPV of US was only 41.9% ($p = 0.06$). US did have an equivalent specificity (100%) and PPV

Table 1 Patient demographics, symptoms, and signs

Demographics, signs, and symptoms	Total (%) $N = 25$
Age at diagnosis	
Mean	7 ± 4.9 years
Range	4 months–17 years
Demographics	
Male	12 (48%)
Female	13 (52%)
Caucasian	15 (60%)
African American	2 (8%)
Hispanic	3 (12%)
Asian	2 (8%)
Other	3 (12%)
Symptoms at onset	
Headache	12 (48%)
Dizziness	3 (12%)
Abdominal pain	2 (8%)
Claudication	3 (12%)
Chest pain or shortness of breath	1 (4%)
Signs at onset	
Hypertension	20 (80%)
Renal bruit	3 (12%)
Aneurysm	2 (8%)
Dissection	1 (4%)
Hyperlipidemia	1 (4%)
Renal infarction	1 (4%)
Renal insufficiency	1 (4%)
History of contraceptive use	1 (4%)

Table 2 Patient initial blood pressures. The number of patients does not add up to 25 since some patients had more than one variant of fibromuscular dysplasia (FMD)

	Mean ± standard deviation	Range
Initial systolic BP (mm Hg)	130.4 ± 27.5	102–228
Initial diastolic BP (mm Hg)	73.56 ± 17.8	48–120
Systolic BP percentiles	89.8 ± 19.4%	46.7%–100%
Diastolic BP percentiles	74.5 ± 25.7%	10.6%–99.9%
Systolic z score	1.24	
Diastolic z score	0.67	

BP blood pressure

*The number of patients does not add up to 25 since some patients had more than one variant of fibromuscular dysplasia (FMD)

Table 3 Imaging of renal arteries

Imaging technique	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Angiography (gold standard)	100 (31/31)	100 (16/16)	100 (31/31)	100 (16/16)
US	28 (7/28)	100 (13/13)	100 (7/7)	41.9 (13/31)
	$p = 0.003$	$p = 0.6$	$p = 0.6$	$p = 0.06$
MRA	62.5 (5/8)	100 (1/1)	100 (5/5)	40 (2/5)
	$p = 0.3$	$p = 0.8$	$p = 0.6$	$p = 0.2$
CTA	84.2 (16/19)	70 (7/10)	84.2(16/19)	70 (7/10)
	$p = 0.4$	$p = 0.4$	$p = 0.4$	$p = 0.4$

*p values are obtained from a comparison with angiography

PPV positive predictive value, *NPV* negative predictive value, *US* ultrasound, *MRA* magnetic resonance angiography, *CTA* computed tomography angiography

(100%). This was true for the specificity and PPV of MRA imaging as well, but MRA imaging showed a lower NPV (40%, $p = 0.2$). This was the lowest NPV of the imaging modalities. However, MRA did show better sensitivity (62.5%, $p = 0.3$) than US. Overall, 3D CTA had the best sensitivity (84.2%, $p = 0.4$) and NPV (70%, $p = 0.4$), but still lacked specificity (70%, $p = 0.4$) and PPV (84.2%, $p = 0.4$) compared with angiography.

Site of the renovascular narrowing

The locations of the various lesions are reported in Table 4. Involvement of the main renal artery was most common and found in 11 patients (26.6% of lesions, $n = 17$ lesions). The renal artery origin was involved in 6 patients (14% of lesions, $n = 9$ lesions). Patients were least likely to have narrowing's involving the hilum, ventral branch, or periphery (each 1.6% of lesions, $n = 1$ lesion). Unifocal disease at a single (45.3%, $n = 29$ lesions) or at multiple sites (15.6%, $n = 10$ lesions) was the most common lesion detected. Involvement at the bifurcation, ventral branch, or renal artery origin showed only unifocal narrowing. On the other hand, involvement at the renal hilum, middle branch, and periphery showed only multifocal narrowing.

Remarkably, 15 narrowed areas (23.4%) were found in the second order or deeper renal arteries. Seven out of the 25 children (28%) had vascular lesions beyond the second renal artery bifurcation that was *only* detected by angiography.

FMD classification

The unifocal FMD variant, at a single site (68%, $n = 17$ children) or multiple sites (28%, $n = 7$ children), was more common than the multifocal variant (11/25 children). Of note, a number of patients were affected by both unifocal and multifocal variants leading to a sum greater than 25.

Discussion

Children treated at CHOP are different in many respects from the first 447 adult patients recorded in the U.S. FMD Registry [16]. There were significantly more males (48 vs. 9%, $p < 0.001$), Hispanics (12 vs. 1.5%, $p = 0.01$), Asians (8 vs. 0.5%, $p = 0.02$), and other races (12 vs. 0.5%, $p = 0.002$) affected by FMD in children than adults. There were also no children who presented with neck pain or pulsatile tinnitus. Children in our cohort had fewer aneurysms (8 vs. 23.5%, $p = 0.8$), lower family history of dyslipidemia (4.3 vs. 56.6%, $p = <0.001$), and less stroke (0 vs. 53.5%, $p = <0.001$) than adults. The minor association of stroke with pediatric FMD is expected in that less than 1% of childhood stroke cases have a diagnosis of FMD [17]. In addition, these children were specifically evaluated in the context of hypertension.

There are similarities between the children and adults in that the majority are Caucasian and the most common presentation is hypertension (80 and 63.8%, $p = 0.2$). A family history of FMD was present in 8.7% of our children and 7.3% of adults although more adults had a family history of hypertension (79 vs. 52%, $p = 0.3$). The strong family history of hypertension suggests that familial inheritance of FMD may be being underdiagnosed. The differences between adults and children noted above raises the question as to what roles genetic, hormonal, and environmental factors play in the epidemiology of FMD. Interestingly, recent genetic studies have found a possible link between FMD and the PHACTR1 gene on chromosome six. The protein encoded by this gene is a member of the phosphatase and actin regulator family of proteins. This protein can bind actin and regulate the reorganization of the actin cytoskeleton [18]. A variant of this gene, rs9349379, has been shown to increase the chances of having FMD by 40% [19].

Three children presented with bruits over the renal artery that was 100% specific for the diagnosis of RAS; however, absence of a bruit does not in any way exclude the diagnosis of RAS. Each bruit was associated with a narrowing of the

Table 4 Site of narrowing

Site of narrowing's	Unifocal narrowing's	Unifocal multiple site narrowing's	Multifocal narrowing's	Total
Main renal	6	5	6	17 (26.6%)
Accessory artery	1	1	2	4 (6.3%)
Renal artery origin	9	0	0	9 (14%)
Renal hilum	0	0	1	1 (1.6%)
Bifurcation	5	0	0	5 (7.8%)
Superior branch	0	0	2	2 (3.1%)
Inferior branch	3	0	1	4 (6.3%)
Ventral branch	1	0	0	1 (1.6%)
Middle branch	0	0	6	6 (9.4%)
2nd order	*1*	*3*	*2*	*6 (9.4%)*
3rd order	*2*	*1*	*2*	*5 (7.8%)*
4th order	*1*	*0*	*2*	*3 (4.7%)*
Periphery	*0*	*0*	*1*	*1 (1.6%)*
Total	29	10	25	64

main renal artery. Evaluation for secondary causes of hypertension lead to the diagnosis of RAS in this cohort.

Computed tomography angiography proved to be the best alternative to angiography with a sensitivity of 84.2% and remains the best non-invasive imaging modality to recognize RAS and renal artery aneurysms [20]. Even so, the sensitivity of CTA and the other imaging modalities is not strong enough to rule out FMD when imaging results are negative. CTA imaging also produced three false negatives (30% of the negative results): one in a superior main renal branch, one in an accessory renal artery, and one in a second order vessel. Accordingly, CTA was less specific (70%) and therefore less likely to correctly label a patient as FMD free. Due to this low specificity, a positive result given by CTA cannot necessarily be used to diagnose a patient with FMD. Adult series have shown similar sensitivities and specificities with ranges of 64–100% and 62–97%, respectively [20–23]. In one pediatric study, the reported sensitivity and specificity were higher at 88 and 81% respectively [20]. Recent studies have demonstrated that full iterative reconstruction techniques of CTA can reduce noise and increase contrast [24–26]. In particular, model-based iterative reconstruction has been reported to improve the accuracy of vessel diameter measurements [25].

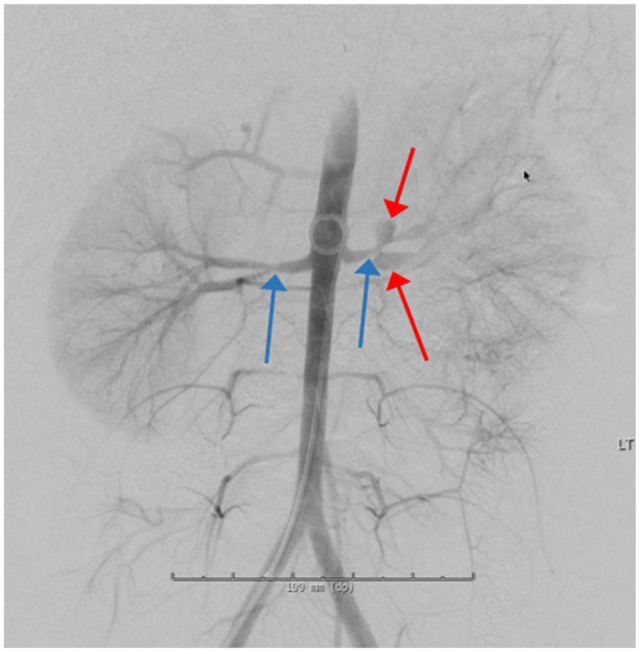

Fig. 1 An example of unifocal fibromuscular dysplasia (FMD) involving multiple sites. Blue arrows point to narrowed areas in the left main renal artery and right renal artery bifurcation, and red arrows point to aneurysms in the superior and inferior branch

Ultrasound is also a poor diagnostic alternative to angiography with a sensitivity of 28%, 38% for main renal artery disease as it fails to identify most children with renovascular disease. Unlike CTA, US produced no false positives and was thus 100% specific. Consequently, a positive result given by US could be confidently used to diagnose a patient with FMD and focus angiographic imaging. Ultrasound is though prone to false negatives and positives and our finding of 100% specificity could be a product of a small sample size [4, 20]. Adult series have shown a much better US sensitivity with a range of 60–100% and comparable specificity with a range from 70 to 100% [20–22]. Some pediatric studies have also shown better sensitivity with a range from 63 to 88% and comparable specificity with a range from 83 to 99% [20]. One pediatric study found US to miss a comparable amount of main RAS with 65% of lesions being missed [20]. Ultrasound is a poor diagnostic tool to diagnose renovascular disease (regardless of the lesions anatomical location); it is beneficial to monitor main renal artery or first order branch pressure and flow following intervention [6]. Contrast-enhanced US has shown further refinement with an improved sensitivity range of 79–100%, a 20% increase in sensitivity

when compared with regular US, and could potentially be used as diagnostic tool for main renal artery FMD [27].

Results show that MRA is a poor alternative modality to angiography as well. The sensitivity of MRA was between that of US and CTA at 62.5%. Similarly, to US, MRA showed no false positives with 100% specificity; thus, positive MRA results could be used confidently. Adult series showed better sensitivity with a range of 90–98% and slightly worse specificity, 70–94% [20–22, 24]. One pediatric study showed improved sensitivity, 80%, and inferior specificity, 63% [15]. As with all the other alternatives, MRA is not a suitable imaging technique to ensure that treatable renovascular disease in children is detected in a timely manner. Of note, a meta-analysis reported that gadolinium-enhanced MRA has shown an improved sensitivity of 97% and could possibly be a more suitable imaging modality [24].

By relying on non-invasive imaging modalities, one might miss the diagnosis of FMD and this may lead to increase severity of hypertension and challenges in controlling hypertension over time and despite CTA being the best noninvasive imaging alternative, angiography is necessary for detection of renovascular disease [6, 9].

Ostial and main renal narrowing was found in 17/25 children (68%). Notably, in 7 out of the 25 patients (28%), FMD occurred in renovascular vessels beyond the first order. In fact, 23.4% of all stenosis were beyond the first order vasculature. Although 23.4% is a significant number of lesions, one retrospective study found 15/24 lesions (62.5%) to be beyond the first order in 21 pediatric patients [28]. This is crucial since the efficacy of all alternative modalities decreases as vessels get smaller. Ultrasound did not show any vascular findings outside of the origin or along the length of the main renal artery (making the imaging technique unsuitable in the diagnosis of 9/25 children). This is expected as US struggles to find lesions in accessory and smaller arteries [20, 21]. Magnetic resonance angiography was incapable of visualizing renovascular disease beyond the first order in children. Computed tomography angiography was accurate up to and including the second order branching of the renal arteries but not beyond.

The unifocal variant (65.4%, $n = 17$ patients) of FMD was the most common lesion seen in these children. This is in contrast to the general population of FMD (mainly adults) where the multifocal variant is the most common lesion but is in accordance with other pediatric studies [4, 10, 28]. Renal artery narrowing beyond the second order branching are not amenable to angioplasty and require medical therapy. The hypertension may be refractory, and careful monitoring of blood pressure and renal function is required especially where there is bilateral distal renovascular disease [2, 6].

Limitations

While all patient records and registry information were available for analysis, there are still some inherent limitations with this study. The first being the sample size. With only 26 patients (25 evaluable), it is less likely that statistically significant differences will be found. The sample used was also biased by including only patients diagnosed with non-inflammatory renovascular disease at CHOP. The patient records were not available for those evaluated for suspected renovascular disease but not diagnosed with FMD. As a result, the specificity, sensitivity, PPV, and NPV apply to children with presumed FMD and may not be generalizable. There may also be referral biases, as patients are often referred to pediatric nephrologist for unexplained hypertension. Lastly, the family histories may not be entirely accurate as FMD was not well documented in the past.

Conclusion

Fibromuscular dysplasia is a more common vascular disease than was previously appreciated and in children seems to primarily affect the renal arteries and their branches. There also seems to be little or no sex predilection in children, unlike in adults. This study provides insight into the limitations of alternative imaging compared with angiography in the diagnosis of presumed renovascular FMD in children. Consequently, we recommend that angiography is done as part of the initial work-up of any child suspected of having renovascular FMD to ensure early detection and appropriate management.

Angiography offers additional visualization of distal vessels and reliable detection of vessel involvement or restenosis. Doppler ultrasound is more commonly used following intervention to monitor flow and branch pressure.

Future research on imaging techniques should focus on improving the sensitivity and specificity of each modality such that angiography is required only to confirm findings and to treat large vessel disease.

Compliance with ethical standards

Written consent was obtained, and the study was approved by the CHOP Internal Review Board (IRB).

Conflict of interest The authors declare that they have no conflict of interest.

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