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Renal angiography in children with polyarteritis nodosa

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Abstract This study describes the angiographic findings in children with polyarteritis nodosa (PAN). Visceral angiograms of 25 children with PAN were reviewed retrospectively by two independent radiologists. In the PAN group, 40% of children had aneurysms demonstrated on selective renal angiography. Most aneurysms affected small and medium-sized arteries. There was agreement between radiologists regarding medium and large aneurysms (K=0.81), but less so for smaller aneurysms. Overall, the presence of medium or large aneurysms was significantly associated with the presence of renal impairment and hypertension. Non-aneurysmal changes were detected more commonly on renal angiography than aneurysms in the PAN group. The most reliable non-aneurysmal signs were perfusion defects, the presence of collateral arteries, lack of crossing of peripheral renal arteries, and delayed emptying of small renal arteries. The sensitivity and specificity of renal angiographic diagnosis of PAN using aneurysms alone was 43% (SE 10%) and 69% (SE 14%) respectively. The sensitivity increased to 80%, and specificity fell to 50% for angiogram positivity defined as the presence of at least one of the most reliable non-aneurysmal signs irrespective of the presence of aneurysms. Aneurysms were also demonstrated on hepatic and mesenteric angiography, and non-aneurysmal signs were found on hepatic, mesenteric, and splenic angiography, although interobserver agreement for angiographic findings in these vascular beds was lower. It is important to consider both aneurysmal and non-aneurysmal angiographic signs, and to include examinations of several vascular beds when utilising angiography for diagnostic purposes in children with PAN.

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Introduction

Polyarteritis nodosa (PAN) was first described by Kussmaul and Maier in 1866 [1]. The original and subsequent descriptions identified the pathologic features of necrotising arteritis with nodules along the walls of medium and small muscular arteries, affecting multiple organ systems throughout the body [2].

The disease is rare in children, and its epidemiology probably imprecise due to poorly defined diagnostic criteria of the illness in the young, and the considerable degree of overlap in the clinical features of the vasculitides in childhood. It has been estimated that less than 150 cases of PAN in the paediatric population had been described by 1976 [3], with several small series reported since [4–9]. The mortality for the condition has been previously reported as 10% for affected children at the Hospital for Sick Children, London [10].

The classical angiographic finding in PAN is aneurysms affecting renal, celiac and coronary arteries [2]. The demonstration of such aneurysms is not, however, pathognomonic of PAN [11]. Also described but less well emphasised are angiographic changes of the smaller order vessels including beaded tortuosity, abrupt cut-offs, tapering stenosis, and pruning of the peripheral vascular tree [12–15]. Albert et al. estimated that when more liberal criteria for positive angiographic findings were applied encompassing these latter non-aneurysmal changes then the sensitivity of a diagnostic strategy involving tissue biopsy and angiography in adults increased from 90% to 95% [16]. Long-term follow-up of these patients did not reveal any false positive angiogram results, and they conclude that a more liberal interpretation of angiography was more accurate than angiogram positivity as defined by the presence of aneurysms alone [12, 16].

The primary aim of this study was to describe retrospectively the angiographic findings in children with a

Table 1 Modified ACR classification criteria for PAN in childhood. The presence of three or more of the criteria will define a patient as having PAN

Criterion	Definition
1. Weight loss of 5% or more, or failure to thrive	Loss of 5% or more of body weight since illness began, not caused by dieting or other factors, or fall-off in weight from the child's normal centile
2. Livedo reticularis	Mottled reticular pattern over the skin of portions of the extremities or torso
3. Testicular pain or tenderness	Pain or tenderness of the testicles, not caused by infection, trauma, or other causes
4. Myalgias, weakness, or leg tenderness	Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles
5. Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy
6. Systemic hypertension	Systolic or diastolic BP greater than age-related reference range
7. Elevated blood urea nitrogen or creatinine	Elevation of BUN or creatinine above age related reference range, not due to dehydration or obstruction
8. Hepatitis B virus infection	Presence of hepatitis B surface antigen or antibody in serum
9. Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of the visceral arteries, not caused by arteriosclerosis, fibromuscular dysplasia, or other non-inflammatory causes
10. Biopsy of small- or medium-sized artery containing polymorphs	Histological changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

diagnosis of PAN. Specific questions relating to the diagnostic sensitivity and specificity of angiography for PAN in this patient group were addressed, as well as the spectrum of angiographic findings (aneurysmal and non-aneurysmal), and the reliability of the proposed individual angiographic signs as measured by interobserver variability.

Materials and methods

Selection of patients

Patients with a clinical diagnosis of PAN at the Great Ormond Street Hospital for Children were identified from clinical and radiological databases. Case notes were reviewed retrospectively and patients fulfilling modified American College of Rheumatology (ACR) classification criteria for PAN [17] were included in the study. The modification of the original ACR criteria for the disease in adults was intended to make the criteria applicable to children, and related to definitions of weight loss, hypertension, and elevation of blood urea nitrogen (BUN) and creatinine. The modified ACR classification criteria are shown in Table 1. As in the adult version, the presence of three or more of the criteria (in the absence of any other diagnosis) defined a patient as having PAN.

Disease controls comprised 11 children who underwent renal angiography for the investigation of non-inflammatory disorders (*N*=11: hypertension of unknown cause *N*=5, hypertension postcoarctation of the aorta *N*=2, renovascular hypertension *N*=1, moyamoya disease *N*=1, phaeochromocytoma *N*=1, hypercalciuria *N*=1). Apart from hypertension, none of these children had any clinical features suggestive of vasculitis.

Review of angiographic data

Two blinded radiologists reviewed the renal and mesenteric angiography of both patient groups independently. Angiograms from the study group were randomly presented to the radiologists along with angiograms from patients with a non-vasculitic diagnosis. Angiographic findings were documented by a third investigator using a pre-designed proforma. The angiographic criteria included on the proforma were established from the literature [2, 12–16], and following discussion with both radiologists and clinicians involved in the study. The angiographic signs examined in the study are shown in Table 2.

Table 2 Description of angiographic findings in PAN

Aneurysmal changes
Small aneurysms – 100–200% of supplying artery calibre
Medium aneurysms – 200–500% of supplying artery calibre
Large aneurysms – >500% of supplying artery calibre
Number of aneurysms
Type of aneurysm: saccular/fusiform
Non-aneurysmal changes
Arterial cut-off
Arterial tapering stenosis
Presence of collateral arteries
Beading of arteries, or other calibre variation
Nephrogram perfusion defects
Lack of crossing of peripheral renal arteries
Pruning of peripheral renal arterial tree
Delayed emptying of arteries
Abnormal persistence of nephrogram

Aneurysm size was expressed as a percentage of the calibre of the supplying artery. The size of vessels manifesting angiographic signs was expressed as a percentage of the calibre of the main renal artery for each patient. A small artery was 0–20% the calibre of the main renal artery; a medium artery 20–50% the calibre of the main renal artery; and a large artery 50–100% (or more) the calibre of the main renal artery.

Analysis of results

Interobserver variability between the radiologists for each angiographic sign was measured using kappa scores [18]. Sensitivity and specificity of renal and mesenteric angiography for the diagnosis of PAN was calculated for angiogram positivity defined by the presence of aneurysms alone, and also for the presence of non-aneurysmal changes, irrespective of the presence of aneurysms. Receiver operator characteristic curves [19] and likelihood ratios [20] were calculated for definitions of angiogram positivity based on the presence of aneurysms alone, and on the presence of aneurysms and/or non-aneurysmal changes. Statistical significance in differences between group findings was determined by the two-sample test of proportion, and the Mann-Whitney U-test.

Results

Twenty-five patients satisfying modified ACR classification criteria for PAN had angiography performed at Great Ormond Street Hospital between 1982 and 1998. Mean age was 7.4 years (range 1.2–14.4 years), with a male to female ratio of 1.2. The mean age of the disease control group was 9.4 years, with a male to female ratio of 1.2. There was no statistical difference in the demography of the patient groups.

Frequency of renal angiographic findings and interobserver variability

The renal angiographic findings and interobserver variability for both groups are shown in Table 3.

Size of renal arteries manifesting angiographic signs

In the PAN group 92% of aneurysms affected small or medium-sized arteries. The remaining 8% affected large arteries. No changes were detected in arteries greater than 100% the calibre of the main renal artery. Ninety percent of non-aneurysmal changes affected small arteries. The remaining 10% affected medium-sized arteries.

Test characteristics of renal angiography for the diagnosis of PAN

Receiver-operator characteristic (ROC) curves were plotted for children with vasculitis based on increasingly liberal definitions of angiogram positivity ranging from the presence of medium or large aneurysms alone, to the presence of only one non-aneurysmal sign irrespective of the presence of aneurysms (Fig. 1). Sensitivity, specificity and likelihood ratios for renal angiography incorporating varying definitions of angiogram positivity are shown in Table 4. When angiogram positivity was defined as the presence of aneurysms (any size) alone, the sensitivity was 43% and specificity 69%. Incorporating the presence of any one of the four non-aneurysmal signs (perfusion defects, collateral arteries, lack of crossing of peripheral renal arteries, and delayed emptying of small renal arteries) which demonstrated positive agreement above chance between the two radiologists (kappa scores

Table 3 Frequency and interobserver agreement (kappa) of renal angiographic findings in PAN patients and disease controls

Renal angiographic sign	PAN (*N*=25, 50 renal units)		Disease control group (*N*=11, 22 renal units)	
	Observed frequency (%)	Kappa score	Observed frequency (%)	Kappa score
Aneurysm of any size	40	0.45	32	0.41
Medium or large aneurysms	15	0.81	0	0.64
Small aneurysms	31	0.14	32	0
Arterial cut-off	38	–0.08	23	–0.21
Arterial tapering stenosis	53	0.02	23	0.28
Presence of collateral arteries	26	0.31	9	0
Arterial beading/other calibre variation	67	–0.06	36	0.27
Nephrogram perfusion defects	65	0.32	27	0.36
Lack of crossing of peripheral renal arteries	67	0.09	36	–0.05
Delayed emptying of arteries	36	0.05	9	0.29
Persistent nephrogram	25[a]	0	0	NA[b]
Pruning of peripheral arterial tree	53	–0.106	32	0

[a] Non-applicable: only 8/25 studies technically adequate to examine the presence or absence of sign
[b] Non-applicable: no studies technically adequate to examine the presence or absence of this sign

Table 4 Sensitivity, specificity, and likelihood ratios for renal angiography diagnosis of PAN using varying definitions of angiogram positivity

Definition of angiogram positivity (presence of at least)	Sensitivity % (SE)	Specificity % (SE)	LR+[a]	LR–[b]
Medium or large aneurysms	16 (7)	87 (10)	1.2	0.9
Aneurysm of any size	43 (10)	69 (14)	1.4	0.8
9 non-aneurysmal changes ± aneurysms	45 (10)	69 (14)	1.5	0.8
8 non-aneurysmal changes ± aneurysms	46 (10)	69 (14)	1.5	0.8
7 non-aneurysmal changes ± aneurysms	48 (10)	69 (14)	1.4	0.8
6 non-aneurysmal changes ± aneurysms	50 (10)	64 (14)	1.4	0.8
5 non-aneurysmal changes ± aneurysms	54 (10)	60 (15)	1.4	0.8
4 non-aneurysmal changes ± aneurysms	65 (10)	50 (15)	1.3	0.8
3 non-aneurysmal changes ± aneurysms	74 (9)	46 (15)	1.4	0.6
2 non-aneurysmal changes ± aneurysms	82 (8)	36 (14)	1.3	0.5
1 non-aneurysmal change ± aneurysms	86 (7)	23 (13)	1.1	0.6

[a] Likelihood ratio for a positive test result
[b] Likelihood ratio for a negative test result

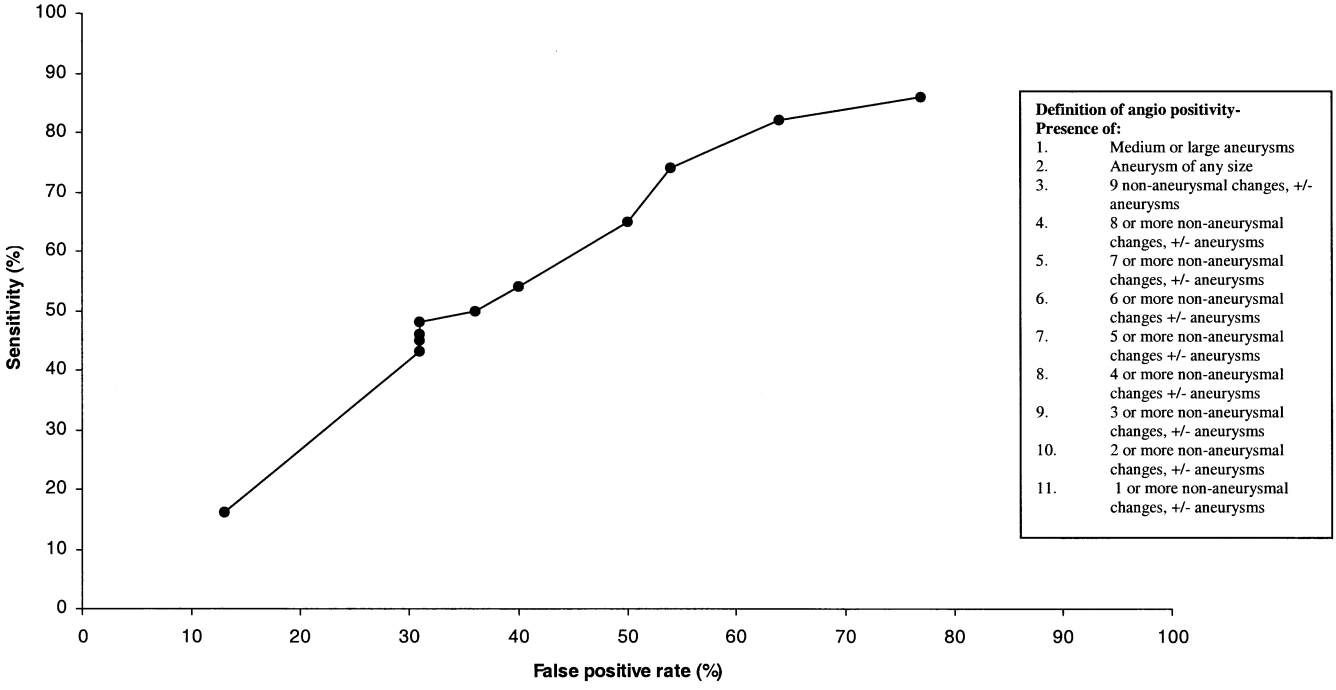

Fig. 1 Receiver-operator characteristic curve for renal angiography diagnostic of PAN. Definitions of angiogram positivity varied from the presence of medium or large aneurysms alone (lowest sensitivity and lowest false positive rate), to increasingly liberal definitions of angiogram positivity incorporating a decreasing number of non-aneurysmal signs. At the most liberal definition the presence of any single non-aneurysmal sign (irrespective of the presence of aneurysms) would result in angiogram positivity for PAN (highest sensitivity and highest false positive rate)

greater than zero) into the definition of angiogram positivity for PAN resulted in an increase in sensitivity to 80% (SE 8%) and a fall in specificity to 50% (SE 15%).

Association of renal angiographic findings with impairment of renal function and hypertension

The percentage of PAN patients with renal impairment was significantly higher in those with medium or large aneurysms than those without (40% vs 5%, $P<0.05$). Renal impairment was also observed more frequently in those with perfusion defects on renal angiography than those without (31% vs 5%), although this did not reach statistical significance. Hypertension occurred more commonly in those with medium or large aneurysms than those without (75% vs 24%, $P<0.05$).

Hepatic, mesenteric and splenic angiography

Overall there was poor agreement between radiologists for the interpretation of hepatic, mesenteric, and splenic angiographic signs. Kappa scores were non-applicable for many of the signs because of small patient numbers (not all the patients had technically adequate angiography of these vascular beds performed). None of the disease controls had angiography of these vascular beds performed.

Small aneurysms affecting small mesenteric arteries were detected with positive agreement ($K=0.63$) in the PAN group. Arterial beading of the small splenic arteries was detected with perfect agreement ($K=1$). One sign observed with weak positive agreement in the hepatic vessels was the presence of abnormally tortuous or "corkscrew" arteries ($K=0.2$). This sign affected small arteries exclusively.

Discussion

There is much debate regarding the gold-standard investigation for PAN. Investigations such as tissue biopsy and visceral angiography are important diagnostic tools for PAN, but neither investigation has sufficient sensitivity or specificity in isolation to operate as a gold standard. Thus previous studies have concentrated on combinations of clinical criteria and investigations to increase diagnostic yield, albeit in adult patients [12, 16, 17]. An important concept worthy of emphasis, however, is that classification criteria are not the same as diagnostic criteria, although the former are often as confused and misused as the latter [21]. Classification criteria work best in the study of groups of patients and work less well in the diagnostic evaluation of individual patients [21]. Indeed, the 1990 ACR criteria for PAN were designed to differentiate PAN from other types of vasculitis, but not to diagnose vasculitis in the first instance [17, 21].

Importantly, the two main classification systems for the vasculitides (the ACR criteria and the Chapel Hill consensus) have never been evaluated in children [22]. There is much debate regarding the most reliable classi-

fication system, with recent studies favouring the Chapel Hill consensus. In this study, we utilised the ACR classification criteria because we believe that the Chapel Hill criteria are less applicable to children than adults since there is a greater degree of overlap in the size of vessel involvement in the childhood vasculitides [22]. Since the Chapel Hill consensus defines a vasculitis based on involvement of the smallest artery manifesting vasculitic changes [23], as such the diagnosis of PAN would be precluded using this system if rash (such as purpura or livedo reticularis – signs of small vessel vasculitis) was present. For the purposes of this study, therefore, we elected to utilise the ACR criteria, which we suggest classified our patients more adequately than the Chapel Hill consensus, but by no means absolutely [17, 21–24]. Indeed, the sensitivity and specificity of the ACR criteria for the classification of PAN in adults are relatively low at 82.2% and 86.6% respectively [11], emphasising the limitations of using such criteria for the classification vasculitis for research purposes.

The classic angiographic finding of aneurysms of medium and small muscular arteries (predominantly affecting the renal and mesenteric arteries) is well documented and accepted as largely diagnostic (although not pathognomonic) of PAN [14, 16, 24]. Well recognised but less emphasised are non-aneurysmal changes affecting the smaller order vessels. Increased awareness of these non-aneurysmal signs could influence the clinical decision-making process and result in earlier treatment of patients with suspected PAN, possibly avoiding permanent end-organ damage or mortality. Non-aneurysmal changes may, however, be regarded as "softer" than the classic aneurysmal changes associated with PAN. Since the result of visceral angiography profoundly influences the decision to treat children with cytotoxic immunosuppressants, it is vital that the test characteristics are optimised with maximal sensitivity and acceptable specificity.

Our results indicate that the inclusion of non-aneurysmal changes in definitions of renal angiogram positivity for PAN results in a progressive rise in the diagnostic sensitivity of the test. If angiogram positivity was defined by the presence of aneurysmal changes (of any size) alone, the sensitivity for PAN diagnosis was 43%. Definitions of angiogram positivity incorporating the presence of non-aneurysmal signs resulted in a progressive rise in sensitivity for PAN diagnosis, reaching 86% for angiogram positivity as defined by the presence of at least one non-aneurysmal sign, irrespective of the presence of aneurysms. The receiver operator characteristic curves also indicate a progressive rise in the false positive rate for angiography with increasingly liberal definitions of angiogram positivity incorporating a decreasing number of non-aneurysmal changes. It must be borne in mind, however, that the angiography was reviewed in a blinded fashion, with neither radiologist being aware of any of the clinical features of the individual patients. Furthermore, some of the loss of angiogram specificity may be the result of overcontrolling in this study since the disease controls were predominantly children with hypertension. It is entirely conceivable that hypertension per se could result in many of the non-aneurysmal angiographic changes described in this study. As such, the disease control patients who were considered as angiogram false positives for vasculitis when the angiography was reviewed blindly (i.e. manifest non-aneurysmal angiographic changes in the absence of vasculitis) had no clinical features suggestive of vasculitis (other than hypertension), and thus the angiographic changes in themselves would not have altered the clinical diagnosis. This emphasises a fundamental general principle of any diagnostic test – the positive predictive value will be higher when applied to groups of patients with a high pre-test probability (prevalence) of disease [21]. Our results do emphasise, however, that the non-aneurysmal angiographic signs observed in our series of children with PAN are not pathognomonic of the disease illustrated by the progressive increase in false-positive rate demonstrated by the ROC curve (Fig. 1), and thus it is vital that clinical features suggestive of vasculitis be used in conjunction with visceral angiography for the diagnosis of PAN in the young.

Table 5 League table of renal angiographic signs in PAN

Angiographic sign	Kappa
Medium and large aneurysms	0.81
Perfusion defects	0.32
Presence of collateral arteries	0.31
Small aneurysms	0.14
Lack of crossing of peripheral renal arteries	0.09
Delayed emptying of renal arteries	0.05

We suggest on the basis of the data presented here that the most reliable (i.e. signs with the least interobserver variability) non-aneurysmal signs were perfusion defects, presence of collateral arteries, lack of crossing of small peripheral renal arteries, and delayed emptying of small renal arteries. Inclusion of these signs in definitions of renal angiogram positivity for PAN resulted in a sensitivity of 80% (SE 8%), a specificity of 50% (SE 15%), a likelihood ratio for a positive angiogram result of 1.6, and a likelihood ratio of a negative angiogram result of 0.4. Based on our results we propose the following "league table" of angiographic signs in PAN (Table 5: most reliable signs at the top of the table). The signs are demonstrated in Fig. 2a and b.

The percentage of patients with renal impairment or hypertension was significantly higher in those with medium or large aneurysms than those without. One important implication of this observation may be that the threshold for performing renal angiography in patients with suspected PAN should be lower for those with renal impairment and/or hypertension.

It has been recognised that vascular beds other than the renal vessels manifest angiographic signs in PAN, and clearly this could be utilised to increase the diagnostic yield of the test [14, 15]. Indeed, Albert et al. argue that the sensitivity of angiography for the diagnosis of

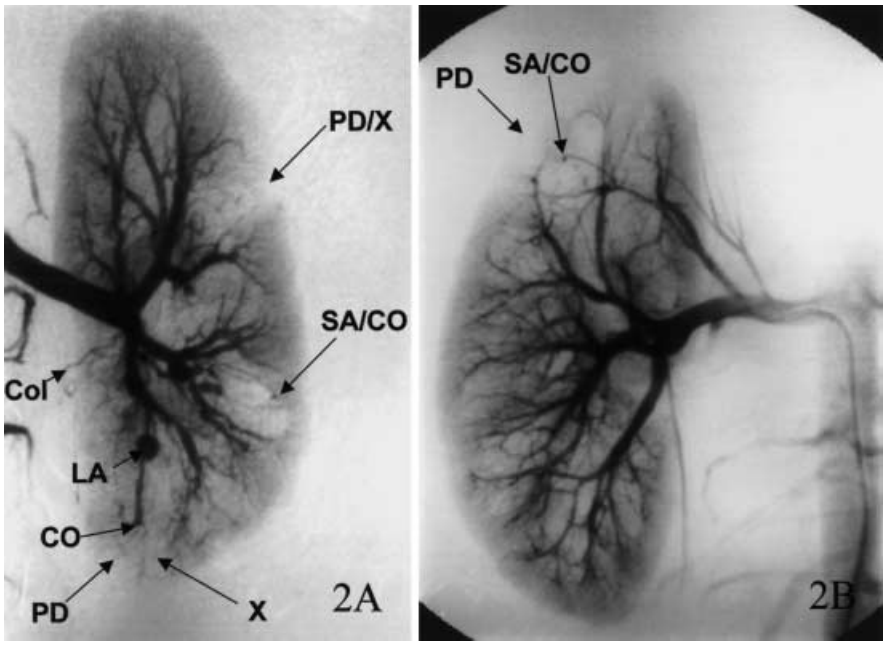

Fig. 2 **A** Renal angiogram from a 6-year-old girl with PAN demonstrating florid aneurysmal and non-aneurysmal changes (*LA* large aneurysms, *SA* small aneurysms, *PD* perfusion defect, *CO* arterial cut-off, *X* lack of crossing of peripheral renal arteries, *Col* collateral artery). **B** Renal angiogram from an 8-year-old boy with PAN demonstrating less florid aneurysmal and non-aneurysmal changes (*PD* perfusion defect, *SA* small aneurysm in association with *CO* arterial cut-off). For the differentiation of small aneurysms from artefact, it is critical that the arterial swelling is visible in both anteroposterior and oblique views

PAN can be increased by visualising each vascular bed sequentially until positive findings are noted [16]. In our series we observed aneurysmal and non-aneurysmal changes of the hepatic, mesenteric, and splenic vascular beds. Although overall agreement for many of the angiographic signs was poor, patient numbers were small so care must be taken in the interpretation of these kappa scores.

Conclusion

Children with PAN manifest a spectrum of angiographic change apart from aneurysms of medium and small-sized arteries, and we have demonstrated that aneurysmal and non-aneurysmal changes affect renal, hepatic, mesenteric and splenic vascular beds. Furthermore we have shown that there is a considerable increase in the sensitivity of renal angiography for the diagnosis of PAN when non-aneurysmal signs are included in definitions of angiogram positivity, although these signs are not pathognomonic of PAN. Lastly, we attempted to quantify the reliability of individual angiographic signs by measuring interobserver variability between two radiologists for each sign, and describe the signs that we consider to be most reliable. It is important, therefore, to consider both aneurysmal and non-aneurysmal angiographic signs, and to include examinations of several vascular beds when utilising angiography for diagnostic purposes in children with suspected PAN.

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