Pediatr Nephrol (1997) 11: 366–372

Pediatric Nephrology

Practical pediatric nephrology

The diagnosis of renovascular disease

Michael J. Dillon

Renal Unit, Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London WC1N 3JH, UK, and Department of Nephrology, Institute of Child Health, Guilford Street, London WC1N 1EH, UK

Received October 14, 1996; received in revised form December 12, 1996; accepted December 16, 1996

Abstract. Renovascular disease is an important cause of remediable hypertension in childhood. Specific diagnostic procedures currently available to investigate affected children include Doppler and computed duplex sonography, angiotensin converting enzyme (ACE) inhibitor sensitisation of radionuclide imaging, captopril-stimulated plasma renin activity, hypotensive responses to ACE inhibitor, renal vein renin measurements, renal angiography and magnetic resonance angiography. Carbon dioxide digital subtraction angiography and computerised tomographic and spiral angiography are also available and may play an important future role in such evaluations. Utilising this array of procedures it is usually possible to define the anatomical and functional status of the renal vasculature and be guided towards the most appropriate therapeutic manoeuvres.

Key words: Renovascular disease – Hypertension – Renin – Duplex sonography – Renography – Captopril – Angiography

Introduction

Renovascular disease, if clinically significant, usually manifests itself as hypertension, although renal arterial abnormalities can be present without an increase in blood pressure. Renovascular hypertension can be defined as hypertension resulting from a lesion (or lesions) that impairs blood flow to a part, or all, of one or both kidneys. It constitutes between 5% and 25% of cases of secondary hypertension in children [1]. In contrast, the prevalence of renovascular disease in unselected hypertensive adults is less than 1% [2]. It presents more commonly in younger children. At paediatric centres seeing substantial numbers of hypertensive children, 8%–10% of patients referred for evaluation and treatment have renovascular disease [3–8]. It is second only to coarctation of the aorta as a cause of surgically remediable hypertension in children [9, 10]. The most common abnormality is some form of renal artery stenosis. It is of historical interest that the first published case of renovascular hypertension treated operatively was a 5.5-year-old boy in whom nephrectomy resulted in normalisation of blood pressure [11].

Correspondence to: M. J. Dillon, Renal Unit, Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London WC1N 3JH, UK

Causes of renovascular disease

The most common condition causing renovascular disease in childhood is fibromuscular dysplasia, which is reported in 70% of patients [9, 10, 12–15]. This is in contrast to the adult situation where 60% of cases of renovascular disease are due to atherosclerosis [15]. Fibromuscular dysplasia predominantly affects the media of the arterial wall. If the intima is the layer most involved, the term intimal hyperplasia is used to describe the appearances. The most characteristic lesions are those causing areas of arterial narrowing alternating with aneurysmal sections, giving rise to a "string of beads" appearance angiographically. The cause is unknown but it might be speculated that uncontrolled release of "growth factors" may play a part. It has been reported as a familial disorder [16] and occurs, especially with intimal hyperplasia, in association with neurofibromatosis [17–21].

Apart from the above, renal artery stenosis is seen in patients with idiopathic hypercalcaemia (William's syndrome) [22], Marfan's syndrome [23], the rubella syndrome [24], Takayasu's disease [25], the Klippel-Trenaunay-Weber syndrome [26] and the Feuerstein-Mims syndrome (linear sebaceous naevus) [6]. Renovascular hypertension has also been reported associated with or following systemic vasculitis and Kawasaki disease [27–29], with renal arteriovenous fistulae [30], renal artery disruption after trauma [9], following neonatal renal artery thrombosis [31] and as a sequel to abdominal radiation [32, 33]. Rarely it is

caused by external compression of the renal arteries by hilar lymph nodes [6] or phaeochromocytoma [34]. Renal tumours, such as Wilms', may also produce hypertension by a similar mechanism, but renin secretion by the tumour may also contribute [35]. Renal artery aneurysms due to fibromuscular dysplasia or following systemic vasculitis or Kawasaki disease can be associated with hypertension [16, 29]. Aneurysmal change is also a manifestation of angiodysplasia, as seen in the Klippel-Trenaunay-Weber syndrome [26]. Renal artery stenosis also occurs post transplantation in approximately 5% of transplant recipients [8, 36].

Anatomical variations

Unilateral main renal artery stenosis may occur in childhood but it is common to see bilateral disease and intrarenal arterial involvement either in association with main artery disease or in isolation [6, 12, 37]. Intrarenal artery disease may affect one or two branch vessels or may present with extensive peripheral renal vascular involvement [9, 38]. Of 54 patients reviewed at the Hospital for Sick Children, London [6], 38 had bilateral renal arterial disease (main arteries alone in 7, main and intrarenal vessels in 13, intrarenal vessels alone in 18). Unilateral disease occurred in 16 patients (main vessels alone in 6, main and intrarenal vessels in 4, isolated intrarenal pathology in 6). Similar findings have been reported in a number of other series from major centres.

It is also well recognised that children with renovascular disease, with or without hypertension, may have extra renal arterial abnormalities, including significant pathology in the mesenteric, splenic and hepatic vessels [6, 39]. A substantial number of these individuals have neurofibromatosis type 1 [8]. Important associations with abdominal coarctation (middle aortic syndrome) [40] and intracranial arterial disease [6, 41] are seen. In the Hospital for Sick Children series, 11 of 54 patients (20%) with renovascular disease had coarctation of the abdominal aorta [6]. Of 16 with neurological symptoms who underwent cerebral angiography, 9 had intracranial arterial disease [6, 41].

Clinical features

There are no pathognomonic symptoms of renovascular disease when a child presents with hypertension. It is also apparent that a substantial number of patients have no symptoms when an increased blood pressure is detected during routine examination. In a recent review of a number of reports in the literature, 60% of children were specifically noted to have no symptoms of hypertension [42]. Clinical examination might reveal evidence of some of the syndromes associated with renovascular disease. In addition, a bruit might be identified over the abdomen, back or elsewhere that might indicate underlying vascular pathology. There are, however, limits to the clinical value of an upper abdominal bruit in identifying renal artery stenosis, with both false-positive and false-negative findings reported [12, 14, 38, 43, 44].

Preliminary diagnostic tests

The majority of children with renovascular disease require preliminary investigations that are common to hypertension in general. When findings compatible with this cause emerge, and other aetiologies have been eliminated, it is possible to embark on specific diagnostic procedures. There are recommended investigative procedures that have been published for the evaluation of children found to be hypertensive [3, 45–48]. These will include routine measurement of plasma electrolytes and renal function, urinalysis and some measure of end organ effect, such as a two-dimensional echocardiogram. An abdominal ultrasound and a 99m technetium-dimercaptosuccinic acid (DMSA) scan give some structural and functional information concerning the kidneys. A peripheral plasma renin activity (PRA) measurement and some measure of plasma or urine catecholamines would complete this preliminary screening.

In children with renovascular disease there may be some degree of hypokalaemia due to secondary hyperaldosteronism, but renal function is usually not impaired unless there is severe renal artery involvement or accelerated hypertension. Urinalysis is usually unremarkable unless there has been "malignant" hypertensive damage to the kidney, when proteinuria and occasionally haematuria may be present. In the majority of children with renovascular hypertension, the peripheral venous PRA levels will be high [49], although approximately 15% of patients with arteriographically proven renal artery stenosis have normal values [42, 50]. It is essential that blood specimens for PRA assays are obtained under standard conditions and interpreted in relation to normal values for age [42, 50]. The refinement of angiotensin converting enzyme (ACE) challenge tests for plasma renin measurements will be dealt with subsequently.

Renal imaging in terms of simple B mode or real-time ultrasonography offers the possibility of identifying the size, shape and echotexture of both kidneys. However, in renovascular disease it is not uncommon to find that on standard ultrasonographic examination no abnormality is detectable. More refined ultrasonographic techniques may, therefore, be needed [51]. DMSA scanning may reveal evidence of renal asymmetry or patchy decreases of isotope uptake within the parenchyma in patients with renovascular disease, as well as entirely normal findings in the presence of marked pathology [51]. Various other radionuclide scanning modalities have also been used for initial screening in children with hypertension, including 99m technetium-diethylenetriamine pentaacetic acid (DTPA) [13, 42, 50]. Without ACE priming, however, only a proportion of children with arteriographically confirmed renal artery stenosis will have abnormalities detected. In the absence of radionuclide scanning facilities, the intravenous urogram utilising the rapid sequence technique may still have a place and provide information suggestive of renal artery stenosis [42]. However, it is not reliable, even with

ACE priming, and although it can supply additional anatomical information it is not recommended if other techniques are available [52].

It is also important to remember the association between renovascular disease and phaeochromocytoma. This can either be due to renal artery compression by tumour or possibly to renal haemodynamic changes as a result of catecholamine release in the vicinity of the kidney [53–56]. PRA may, therefore, be increased in the presence of a phaeochromocytoma and urine and plasma catecholamines may be increased in the presence of renovascular disease.

Specific tests for the diagnosis of renovascular hypertension

Further investigations for renovascular disease would be justified if there was no evidence of an alternative explanation for the hypertension, and if the investigative findings were compatible with a renin-dependent hypertensive state without obvious cause. Additional investigative procedures might include Doppler ultrasonography, computed duplex sonography, ACE inhibitor sensitisation of radionuclide imaging techniques, captopril-stimulated PRA, hypotensive responses to ACE inhibition, renal vein renin measurements, renal angiography, magnetic resonance angiography, carbon dioxide (CO_2) digital subtraction angiography, computerised tomographic angiography and spiral angiography [57]. How far these investigations should be taken would depend on the severity of the hypertension, the ease of pharmacological control, the age of the child and the likelihood of some therapeutic benefit arising as a result.

Doppler and computed duplex sonography

Doppler ultrasonography can be used to demonstrate changes in flow in renal arteries due to stenotic lesions [58, 59]. Computed duplex sonography can measure blood flow velocities and absolute renal blood flow volume [60]. The sensitivity and specificity of these tests for renal artery stenosis have been of the order of 84%–100% and 73%–98.5%, respectively [61–65]. However, even in experienced hands, 20% of studies are technically unsatisfactory and, hence, have limited application. Nonetheless, as a non-invasive test for initial assessment of renovascular disease and in monitoring results of corrective surgery, duplex Doppler ultrasonography has some role [61]. In the detection of renal artery stenosis in transplant patients it has been shown to be associated in the majority, but not all studies, with a high sensitivity [66–68] and a specificity of 75% [68]. In addition, Garel et al. [69] have utilised intrarenal Doppler ultrasonography in an attempt to predict curability of renovascular hypertension. They showed that a negative intrarenal Doppler ultrasound result can be predictive of cure with endovascular therapy or surgery [69]. Others have supported the use of this type of technology for identifying renal artery stenosis in native and transplanted kidneys, but emphasise its limitations. It unquestionably diagnoses stenotic lesions only when they are severe [70].

ACE inhibitor renography

Refinements of radionuclide imaging techniques, particularly utilising ACE inhibitor sensitisation to unmask main renal artery or major branch artery stenosis, have also proved helpful in renovascular disease [52, 71–77]. These utilise the principle that a reduced renal perfusion pressure, due to renal artery stenosis, results in angiotensin 2-mediated efferent arteriolar vasoconstriction to maintain glomerular filtration rate (GFR) and that the ACE inhibition reduces this postglomerular efferent resistance. The effect of this is that the GFR distal to the stenosis is decreased and individual kidney function can be assessed non-invasively using radionuclide studies [78]. A number of radiopharmaceuticals have been used for this purpose including DTPA, ^{123}iodine (I) and ^{131}I-orthoiodohippurate, 99m technetium-mercaptoacetyl glycyl glycyl glycine (MAG-3) and DMSA, with captopril being used most often as the ACE inhibitor [52, 77, 78]. The sensitivity and specificity rates for ACE inhibitor renography in renovascular disease of adults has been of the order of 90% [52]. Diagnostic criteria are not standardised and hence interpretation of data is complex. However, an assessment of both the scintigraphic images and the computer-generated time curves provides useful information. Utilising these data it is possible to identify patients with renovascular hypertension as well as, in some series, providing predictions on the blood pressure response following surgical or angioplastic intervention [52, 61, 77, 78].

Such techniques have mainly been utilised in adults and there are limited data in children. Minty et al. [79], however, have shown that, compared with renal angiography, captopril-primed DMSA scans gave a sensitivity of 80% and a specificity of 89% of the renal pathology being due to renovascular disease.

Captopril-stimulated PRA

Some have used the peripheral blood renin responsiveness to administered captopril as a means of diagnosing renovascular disease in hypertensive patients [52, 80]. This followed the report in 1979 by Case et al. [81] of marked increases in peripheral PRA in patients with renovascular hypertension after angiotensin blockade. There are two studies that have reported the use of this technique in children. Hamed et al. [82] concluded that it might distinguish renovascular disease from other causes of hypertension. The study of Gauthier et al. [83] found the predictive value of a positive test to be only 43% and concluded that it was not sufficiently accurate to be used as a screening test.

Hypotensive response to ACE inhibition

Instead of measuring the change induced in plasma renin levels following ACE inhibition, some have studied the

hypotensive response to captopril [84, 85]. Daman-Willems et al. [85] showed in children that a 10% fall of mean systolic blood pressure or a 15% fall of diastolic blood pressure after a single oral dose of captopril was significantly correlated with the initial PRA. They concluded that the technique did have value in screening for renin-dependent hypertension in children.

Renal vein renin measurements

Selective main and segmental renal vein renin sampling have proved valuable in paediatric practice [1, 6, 86–88]. These techniques allow lateralisation of the kidney from which renin release is occurring and identification, from the segmental veins within the renal parenchyma, of the origins of local sources of renin release. This is in contrast to the majority of papers concerning adults in which a lack of sensitivity and specificity has been reported [61]. The technique may be particularly helpful in renovascular disease in children with its high incidence of bilateral intrarenal arterial disease making for diagnostic difficulties. In addition, some predictive information concerning surgical or interventional radiological treatment can be obtained. This might be possible, for example, by demonstrating excess renin release from one kidney and lack of release from the contralateral side which, in unilateral disease, would be the normal kidney. Ratios of more than 1.5 between values in the main renal veins are considered significant and predict a positive response to surgery, especially if a ratio of less than 1.3 exists between the contralateral kidney and the low inferior vena cava value [86, 88]. This latter finding points to suppression of the less-affected or normal kidney.

However, there are a number of reasons why renal vein renin levels may fail to demonstrate lateralisation in the presence of haemodynamically significant renal artery stenosis [42]. These might include technical errors, bilateral disease and segmental artery involvement. Segmental vein sampling might overcome the last of these, but is technically challenging, especially in small children, and samples may not be precisely from the same areas affected by the arterial lesions [88]. When undertaking such studies, there needs to be careful standardisation of the technique and handling of samples, as well as a knowledge of the normal range of ratios in children without renal arterial disease [89]. Stimulation of renin release by frusemide [12] and captopril [90] have their advocates, with claims of improved accuracy, but there are some risks of change of renin release with time that can make for difficulties in interpretation.

Renal angiography

Renal vein renin studies are usually coupled with selective renal angiography [58, 86, 91], which nowadays utilises intraarterial digital methodology as opposed to conventional contrast technology [92]. This would normally involve a flush aortogram, followed by selective renal arteriography with angled views utilising non-ionic contrast medium. It has to be stressed that this, coupled with a renal vein renin study, is a skilled, invasive and expensive investigation not to be embarked on too lightly. However, it is the definitive study and currently the “gold standard” for diagnosing renovascular disease in children. If surgical or invasive radiological treatment is being considered, it is still mandatory to precede it with angiography.

Intravenous digital angiography was heralded as a means of less invasively investigating patients with presumed renovascular pathology, but has not really lived up to expectation. Although it might demonstrate the main renal arteries, it fails to adequately visualise the major branches or the intrarenal vasculature that are so frequently affected in childhood [93, 94]. In view of the association with extra renal arterial disease, cerebral angiography is also required at times, especially in the presence of cranial bruits or neurological complications [6, 41]. Occasionally, indirect information concerning cerebral arterial pathology can be obtained by undertaking functional studies of cerebral blood flow. An example of such a technique is the 99m technetium-hexamethyl propyleneamine oxide scan, which might indicate the presence of intracranial disease [57].

Magnetic resonance angiography

Magnetic resonance angiography is full of promise in childhood renovascular disease, but awaits full evaluation. Currently, it only seems valuable in detecting pathology in the main renal artery or its major branches [95–97]. It is, therefore, a less-attractive tool in paediatric practice. It does, however, have a role in terms of defining the normality or otherwise of the major vessels, and clearly can be useful in post-transplant renal arterial stenosis [98].

CO_2 digital subtraction angiography

Other techniques may be of value in paediatric practice in due course and that involving the use of digital subtraction angiography with CO_2 as an intravascular contrast agent is a case in point [99, 100]. This has proved to be safe and clinically useful in adults, especially those with concomitant renal insufficiency or a history of iodinated contrast reaction [101–103]. It remains to be seen whether it might be applied equally safely to children.

Computerised tomographic and spiral angiography

Computerised tomographic angiography and spiral angiography also hold enormous potential for the investigation of renal arterial disease and have been utilised, to an extent, in adult practice [104–107], but much less frequently in paediatrics. Current constraints in terms of routine use centre around the requirement of a substantial contrast bolus and the interpretation of the three-dimensional images. Nonetheless, it may have a major impact in due course on our investigative procedures for childhood renovascular hypertension.

Conclusion

It can be seen that the refined diagnostic techniques currently available allow for a quite-sophisticated approach to be taken when evaluating children suspected of renovascular disease. The mainstay of this approach, however, relies on well-tried techniques, including ultrasonography, isotope scanning with and without captopril priming, peripheral and renal vein renin measurements and intraarterial digital subtraction angiography. Utilising this array of procedures, it is usually possible to define the anatomical and functional status of the renal vasculature and the kidneys and be guided into the most appropriate therapeutic manoeuvre to improve or cure the raised blood pressure. It remains to be seen if the newer investigative tools, including magnetic resonance angiography, CO_2 angiography or computerised tomographic and spiral angiography, will improve the handling of affected children and allow for more precise diagnostic information without added risk.

References

1. Watson AR, Balfe JW, Hardy BE (1985) Renovascular hypertension in childhood: a changing perspective in management. J Pediatr 106: 366–372
2. Berglund G, Andersson O, Wilhelmsen L (1976) Prevalence of primary and secondary hypertension: studies in random population sample. BMJ 2: 554–556
3. Dillon MJ (1987) Investigation and management of hypertension in children. Pediatr Nephrol 1: 59–68
4. Lieberman E (1990) Hypertension in childhood and adolescence. In: Kaplan NM (ed) Clinical hypertension. Williams and Wilkins, Baltimore, p 407
5. Loirat C, Pillion G, Blum C (1982) Hypertension in children: present data and problems. Adv Nephrol 11: 65–98
6. Deal JE, Snell ME, Barratt TM, Dillon MJ (1992) Renovascular disease in childhood. J Pediatr 25: 55–65
7. Arar MY, Hogg RJ, Arant BS, Seikaly MG (1994) Etiology of sustained hypertension in children in the South Western United States. Pediatr Nephrol 8: 186–189
8. Ingelfinger JR (1993) Renovascular disease in children. Kidney Int 43: 493–505
9. Fry WJ, Ernst CB, Stanley JC, Brinnk B (1973) Renovascular hypertension in the pediatric patient. Arch Surg 107: 692–698
10. Stanley JC (1992) Surgical intervention in pediatric renovascular hypertension. Clin Nephrol Urol 12: 167–176
11. Leadbetter WF, Burkland CE (1938) Hypertension in unilateral renal disease. J Urol 39: 611–626
12. Lawson JB, Boerth R, Foster JH, Dean RH (1977) Diagnosis and management of renovascular hypertension in children. Arch Surg 122: 1307–1316
13. Stanley P, Gyepes MT, Olsen DL, Gates GF (1978) Renovascular hypertension in children and adolescents. Radiology 129: 123–131
14. Makker SP, Moorthy B (1979) Fibromuscular dysplasia of renal arteries. An important cause of renovascular hypertension in children. J Pediatr 95: 940–945
15. Wise KL, McCann RL, Dunnick NR, Paulson DF (1988) Renovascular hypertension. J Urol 140: 911–924
16. Kaufmann JJ, Goodwin WE, Waisman J, Gyepes MT (1972) Renovascular hypertension in children. Report of seven cases treated surgically including two cases of renal auto transplantation. Am J Surg 124: 149–157
17. Leumann EP (1979) Blood pressure and hypertension in childhood and adolescence. Ergeb Inn Med Kinderheilkd 43: 109–183
18. Halpern M, Currarino G (1965) Vascular lesions causing hypertension in neurofibromatosis. N Engl J Med 273: 248–252
19. Mena E, Bookstein JJ, Holt JF, Fry WJ (1973) Neurofibromatosis and renovascular hypertension in children. Am J Roentgenol 118: 39–45
20. Green JF, Fitzwater JE, Burgess J (1974) Arterial lesions associated with neurofibromatosis. Am J Clin Pathol 62: 481–487
21. Muller-Wiefel DE (1978) Renovasculare hypertension bei neurofibromatose von Recklinghausen. Monatsschr Kinderheilkd 126: 113–118
22. Wiltese HE, Goldbloom RB, Asuquo AU, Antina AU, Ottesen OE, Rowe RD, Cooke RE (1966) Infantile hypercalcaemia syndrome in twins. N Engl J Med 275: 1157–1160
23. Loughridge LW (1959) Renal abnormalities in the Marfan syndrome. Q J Med 531–544
24. Menser MA, Dorman DC, Reye RDK, Reid RR (1966) Renal artery stenosis in the rubella syndrome. Lancet I: 790–792
25. Wiggelinkhuizen J, Cremin BJ (1978) Takayasu arteritis and renovascular hypertension in childhood. Pediatrics 62: 209–217
26. Proesmans W (1982) Syndrome de Klippel-Trenaunay avec hypertension arterielle et insuffisance renale chronique. Ann Pediatr (Paris) 29: 671–674
27. White RH, Schambelan M (1980) Hypertension, hyperreninemia and secondary hyperaldosteronism in systemic necrotizing vasculitis. Ann Intern Med 92: 199–201
28. Daniels SR, Loggie JMH, McEnery PT, Towbin RB (1986) Clinical spectrum of intrinsic renovascular hypertension in children. Pediatrics 80: 698–704
29. Inoue O, Akagi T, Ichinose E, Kato H (1988) Systemic artery involvement in Kawasaki disease. In: Kawasaki T (ed) Proceedings of the Third International Kawasaki Disease Symposium. Japan Heart Foundation, Tokyo, p 262
30. Palmer JM, Connolly JE (1966) Intrarenal arteriovenous fistula: surgical excision under selective renal hypothermia with kidney survival. J Urol 96: 599–605
31. Adelman RD (1978) Neonatal hypertension. Pediatr Clin North Am 25: 99–110
32. O'Malley B, D'Angio GJ, Vawter GF (1963) Late effects of roentgen therapy given in infancy. Am J Roentgenol 89: 1067–1074
33. Koskimies O (1988) Arterial hypertension developing 10 years after radiotherapy for Wilm's tumour. BMJ 285: 996–998
34. Alvestrand A, Bergström J, Wehle B (1977) Pheochromocytoma and renovascular hypertension. A case report and review of the literature. Acta Med Scand 202: 231–236
35. Spahr J, Demers LM, Shochat SJ (1981) Renin producing Wilm's tumour. J Pediatr Surg 16: 32–34
36. Rosenblum ND, Ingelfinger JR (1992) Hypertension in children with chronic renal insufficiency. In: Loggie JMH (ed) Pediatric and adolescent hypertension. Blackwell, Oxford, p 239
37. Guzzeta PC, Davis CF, Ruley EJ (1991) Experience with bilateral renal artery stenosis as a cause of hypertension in childhood. J Pediatr Surg 26: 532–534
38. Korobkin M, Perloff DL, Palobniskas AJ (1976) Renal arteriography and the evaluation of unexplained hypertension in children and adolescents. J Pediatr 88: 388–393
39. Luscher TF, Keller HM, Imhof HG, Greminger P, Kuhlman U, Largiader F, Schneider E, Schneider J, Vetter W (1986) Fibromuscular hyperplasia: extension of the disease and therapeutic outcome. Nephron 44 [Suppl 1]: 109–114
40. Sumboonnanonda A, Robinson BL, Gedroyc WMW, Saxton HM, Reidy JF, Haycock GB (1992) Middle aortic syndrome: clinical and radiological findings. Arch Dis Child 67: 501–505
41. Daman Willems CD, Salisbury DM, Lumley JSP, Dillon MJ (1985) Brain revascularisation in hypertension. Arch Dis Child 60: 1177–1179
42. Hiner LB, Falkner B (1993) Renovascular hypertension in children. Pediatr Clin North Am 40: 123–140
43. Coran AG, Schuster SR (1968) Renovascular hypertension in childhood. Surgery 64: 672–677

44. Leumann EP, Bauer RP, Slaton PE, Biglieri EG, Holliday MA (1970) Renovascular hypertension in children. Pediatrics 46: 362–370
45. Robson AM (1978) Special diagnostic studies for the detection of renal and renovascular forms of hypertension. Pediatr Clin North Am 25: 83–98
46. Kaplan RA, Hellerstein S, Alan U (1992) Evaluation of the hypertensive child. Child Nephrol Urol 12: 106–112
47. Loggie JMH (1992) Evaluation of the hypertensive child and adolescent. In: Loggie JMH (ed) Pediatric and adolescent hypertension. Blackwell, Oxford, p 112
48. Ingelfinger JR, Dillon MJ (1994) Evaluation of secondary hypertension. In: Holliday MA, Barratt TM, Avner ED (eds) Pediatric nephrology, 3rd edn. William and Wilkins, Baltimore, p 1146
49. Dillon MJ, Ryness JM (1975) Plasma renin activity and aldosterone concentration in children. BMJ 4: 316–319
50. Guzzetta PC, Potter BM, Ruley EJ, Majd M, Bock GH (1989) Renovascular hypertension in children. Current concepts in evaluation and treatment. J Pediatr Surg 24: 1236–1240
51. Gordon I (1994) Imaging the kidneys and urinary tract. In: Holliday MA, Barratt TM, Avner ED (eds) Pediatric nephrology, 3rd edn. Williams and Wilkins, Baltimore, p 421
52. Jonker GJ, Huisman RM, Zeeuw D de (1993) Enhancement of screening tests for renovascular hypertension by angiotensin converting enzyme inhibitors. Nephrol Dial Transplant 8: 798–807
53. Robinson MJ, Kent M, Stoeks J (1973) Phaeochromocytoma in childhood. Arch Dis Child 48: 137–142
54. Rosenheim ML, Ross EJ, Wrong OM, Hodson CJ, Davis DR, Smith JF (1963) Unilateral renal ischaemia due to compression of a renal artery by a pheochromocytoma. Am J Med 34: 735–748
55. Hiner LB, Gruskin AB, Baluarte HJ, Cole ML, Sapire DWR, Levitsky D (1967) Plasma renin activity and intra renal blood flow distribution in a child with a pheochromocytoma. J Pediatr 89: 950–952
56. Melicow MM (1977) One hundred cases of pheochromocytoma (107 tumors) at the Columbian Presbyterian Medical Center 1926–1976. Cancer 40: 1987–2004
57. Dillon MJ, Deal JE (1996) Renovascular hypertension in children. In: Novick AC, Scoble J, Hamilton G (eds) Renal vascular disease. Saunders, London, p 235
58. Tapper D, Brand T, Hickman R (1987) Early diagnosis and management of renovascular hypertension. Am J Med 153: 495–500
59. Siegel MJ, Amour TES, Siegel BA (1987) Imaging techniques in the evaluation of pediatric hypertension. Pediatr Nephrol 1: 76–88
60. Rosendahl W, Grunert D, Schoning M (1994) Duplex sonography of renal arteries as a diagnostic tool in hypertensive children. Eur J Pediatr 153: 588–593
61. Wilkinson R (1994) Renal and renovascular hypertension. In: Swales JD (ed) Textbook of hypertension. Blackwell, Oxford, p 831
62. Handa N, Fukanaga R, Ogawa S, Matsumoto M, Kimura K, Kamada T (1988) A new accurate and non invasive screening method for renovascular hypertension: the renal Doppler technique. J Hypertens 6 [Suppl 4]: S458–S460
63. Taylor DC, Kettler MD, Moreta GL, Kohler TR, Kazmers A, Beach KW, Strandness DE (1988) Duplex ultrasound scanning in the diagnosis of renal artery stenosis – a prospective evaluation. J Vasc Surg 7: 363–369
64. Hawkins PG, McKnoulty LM, Gordon RD, Klemm SA, Tunny TJ (1989) Non invasive renal artery duplex ultrasound and computerized nuclear renography to screen for and follow progress in renal artery stenosis. J Hypertens 7 [Suppl 6]: S184–S185
65. Zoller WG, Hermans H, Bogner JR, Hahn D, Middeke M (1990) Duplex sonography in the diagnosis of renovascular hypertension. Klin Wochenschr 68: 830–834
66. Erly CM, Duda SH, Wakat JP, Sökler M, Reuland P, Müller-Schauenburg W, Schareck W, Lauchart W, Risler T (1992) Non invasive procedures for diagnosis of renovascular hypertension in renal transplant recipients – a prospective analysis. Transplantation 54: 863–867
67. Plainfosse MC, Calonge VM, Beyloune-Mainardi C, Glotz D, Duboust A (1992) Vascular complications in the adult kidney transplant recipient. J Clin Ultrasound 20: 517–527
68. Glicklich D, Tellis VA, Quinn T, Mallis M, Greenstan SM, Schechner R, Heller S, Freeman LM, Kutcher R, Veith FJ (1990) Comparison of captopril and Doppler ultrasonography as screening tests for transplant renal artery stenosis. Transplantation 49: 217–219
69. Garel L, Dubois J, Robitaille P, Russo P, Filiatrault D, Grignon A, Dube J (1995) Renovascular hypertension in children: curability predicted with negative intrarenal Doppler US results. Radiology 195: 401–405
70. Toma P, Lucigrai G, Magnano G, Gusmano R, Piaggio G (1994) Intraparenchymal renal doppler: the indirect signs of renal artery stenosis in native and transplanted kidneys in childhood. Radiol Med (Torino) 88: 244–248
71. Sfakianakis GN, Bourgoigne JJ, Jaffe D, Kyriakides G, Perez-Stable E, Duncan RC (1987) Single dose captopril scintigraphy – an advance in the detection and treatment of renovascular hypertension. J Nucl Med 28: 1383–1392
72. Meier GH, Sumpio B, Black HR, Gusberg RJ (1990) Captopril renal scintigraphy – an advance in the detection and treatment of renovascular hypertension. J Vasc Surg 11: 770–777
73. Fommei F, Bellina R, Bertelli P, Gazzetti P, Palla L, Ragazzini A, Ghione S (1987) Interactive functional imaging of renal scintigraphy after captopril in the detection of global or segmental hypoperfusion. Contrib Nephrol 56: 111–116
74. Fommei E, Mezzasalma L, Ghione S, Volterrani D, Oei Y, Hilson AJ, Carrieri M (1991) European captopril radionuclide test multicentre study. Preliminary results. Inspective renographic analysis. Am J Hypertens 4: 690S–697S
75. McLean AG, Hilson AJ, Scoble JE, Maher ER, Thakrar DS, Moorhead JF, Sweny P (1992) Screening for renovascular disease with captopril enhanced renography. Nephrol Dial Transplant 7: 211–215
76. Dondi M (1991) Captopril renal scintigraphy with 99mTc mercaptoacetyl triglycine (^{99m}Tc-MAG3) for detecting renal artery stenosis. Am J Hypertens 4: 737S–740S
77. Pedersen EB (1994) Angiotensin converting enzyme inhibitor renography. Pathophysiological, diagnostic and therapeutic aspects in renal artery stenosis. Nephrol Dial Transplant 9: 482–492
78. Nally JV (1996) Captopril renography. In: Novick AC, Scoble J, Hamilton G (eds) Renal vascular disease. Saunders, London, p 195
79. Minty I, Lythgoe MF, Gordon I (1993) Hypertension in paediatrics: can pre and post captopril technetium 99m dimercaptsuccinic acid scans exclude renovascular disease. Eur J Nucl Med 20: 699–702
80. Pickering TG (1996) Peripheral and renal vein renin testing. In: Novick AC, Scoble J, Hamilton G (eds) Renal vascular disease. Saunders, London, p 185
81. Case DB, Atlas SA, Laragh JH (1979) Reactive hyper reninaemia to angiotensin blockade identifies renovascular hypertension. Clin Sci 57: 313s–316s
82. Hamed RMA, Balfe JW, Ellis G (1990) The use of the captopril test to assess renin responsiveness in children with hypertension and renal disease. Child Nephrol Urol 10: 181–185
83. Gauthier B, Trachtman H, Frank R, Pillari G (1991) Inadequacy of captopril challenge tests for diagnosing renovascular hypertension in children and adolescents. Pediatr Nephrol 5: 42–44
84. Hodsman GP, Isles CG, Murray GD, Webb DJ, Robertson JJ (1983) Factors related to first dose hypotensive effect of captopril: prediction and treatment. BMJ 286: 832–834
85. Daman Willems CD, Shah V, Uchiyama M, Dillon MJ (1989) The captopril test; an aid to investigation of hypertension. Arch Dis Child 4: 229–234
86. Stringer DA, Bruyn R de, Dillon MJ, Gordon I (1984) Comparison of aortography, renal vein renin sampling, radionuclide scans, ultrasound and the IVU in the investigation of childhood renovascular hypertension. Br J Radiol 57: 111–121

87. Godard C (1977) Predictive value of renal-vein renin measurements in children with various forms of renal hypertension: an international study. Helv Paediatr Acta 32: 49–57
88. Dillon MJ, Shah V, Barratt TM (1978) Renal vein renin measurements in children with hypertension. BMJ 2: 168–170
89. Gerdts K, Shah V, Savage JM, Dillon MJ (1979) Renal vein renin measurements in normo tensive children. J Pediatr 95: 953–958
90. Tomoda F, Takata M, Ohashi S, Ueno H, Ikeda K, Yasumoto K, Iida H, Sassayama S (1990) Captopril stimulated renal vein renin in hypertensive patients with or without renal artery stenosis. Am J Hypertens 3: 918–926
91. Tonkin IL, Stapleton BF, Roy S (1988) Digital subtraction angiography in the evaluation of renal vascular hypertension in children. Pediatrics 81: 150–158
92. Kim D, Porter DH, Brown R, Crivello MS, Silva P, Leeming BW (1991) Renal artery imaging: a prospective comparison of intra arterial digital subtraction angiography with conventional angiography. Angiology 42: 345–357
93. Wilms GE, Baert AL, Staesson JA, Amery AK (1986) Renal artery stenosis: evaluation with intravenous digital subtraction angiography. Radiology 160: 713–715
94. Mann SJ, Pickering TG (1992) Detection of renovascular hypertension. State of the art. Ann Intern Med 117: 845–853
95. Stark DD, Bradley WG (1991) Magnetic resonance imaging, 2nd edn. Mosby, St Louis
96. Debatin SF, Spritzer CE, Crist TM, Beam C, Svetkey LP, Newman GE, Sostman HD (1991) Imaging of renal arteries: value of MR angiography. Am J Roentgenol 157: 981–990
97. Gedroyc W (1996) Magnetic resonance angiography of renal arteries. In: Novick AC, Scoble J, Hamilton G (eds) Renal vascular disease. Saunders, London, p 91
98. Gedroyc W, Negus R, Al-Kutoubi A, Palmer A, Taube D, Hulme B (1992) Magnetic resonance angiography of renal transplants. Lancet 339: 789–791
99. Hawkins IF (1982) Carbon dioxide digital subtraction angiography. Am J Roentgenol 139: 19–24
100. Kerns SR, Hawkins IF (1996) Carbon dioxide angiography. In: Novick AC, Scoble J, Hamilton G (eds) Renal vascular disease. Saunders, London, p 107
101. Weaver FA, Pentecost MJ, Yellin AE, Davis S, Fink E, Teitelbaum G (1991) Clinical applications of carbon dioxide/digital subtraction arteriography. J Vasc Surg 13: 266–273
102. Miller FJ, Mineau DE, Koehler PR, Davis S, Fink E, Teitelbaum G (1983) Clinical intra arterial digital subtraction imaging. Radiology 148: 273–278
103. Seeger JM, Self S, Harward TRS, Flynn TC, Hawkins IF (1993) Carbon dioxide gas as an arterial contrast agent. Ann Surg 217: 688–698
104. Rubin GD, Dake MD, Napel SA, McDonnell CH, Jeffrey RB (1993) Three dimensional spiral CT angiography of the abdomen: initial clinical experience. Radiology 186: 147–152
105. Galinski M, Prokop M, Chavan A, Schaefer CM, Jandeleit K, Nischelsky JE (1993) Renal artery stenoses: spiral CT angiography. Radiology 189: 85–92
106. Rubin GD, Dake MF, Napel S, Jeffrey RB Jr, McDonnell CH, Sommer FG, Wexler L, Williams DM (1994) Spiral CT of renal artery stenosis: comparison of three-dimensional rendering techniques. Radiology 190: 181–189
107. Platts AD (1996) CT angiography and spiral angiography. In: Novick AC, Scoble J, Hamilton G (eds) Renal vascular disease. Saunders, London, p 143

Literature abstract

Kidney Int (1996) 50: 1990–2001

Urinary IL-6/EGF ratio: a useful prognostic marker for the progression of renal damage in IgA nephropathy

E. Ranieri, L. Gesualdo, F. Petrarulo, and F. P. Schena

Interleukin 6 (IL-6) is produced by human mesangial and tubular cells, and its urinary levels has been proposed as a marker of mesangial proliferation and tubulointerstitial damage. Epidermal growth factor (EGF) is expressed within the Henle's loop and the distal tubule and has been shown to accelerate recovery from renal injury. In the present study we have defined renal gene and protein expression of IL-6 and EGF in 10 normal, 10 nonproliferative glomerulonephritis (NPGN) and 30 IgA nephropathy (IgAN) human kidneys by RT-PCR, in situ hybridization and immunohistochemical techniques. Moreover, urinary IL-6 and EGF levels were measured in 41 patients with IgAN and in 20 normal subjects (N). In normal kidneys, EGF was localized in Henle's loop and distal convoluted tubule whereas IL-6 was mainly located in the proximal tubule and, less, within the glomerulus. In IgAN patients, EGF was decreased whereas IL-6 expression was upregulated. These modifications paralleled the degree of tubulointerstitial damage. Moreover, IgAN patients as a whole exhibited a reduction of EGF and an increase of IL-6 urinary concentration (EGF values: N, 12.96 ± 1.15; IgAN Grades 1–2, 20.05 ± 2.64; Grades 3–4, 7.60 ± 1.70; Grade 5, 3.14 ± 0.71, ng/mg urinary creatinine. IL-6 values: N, 2.04 ± 0.51; IgAN Grades 1–2, 3.26 ± 0.38; Grades 3–4, 5.67 ± 0.92; Grade 5, 27.20 ± 9.70 pg/mg urinary creatinine), that correlated with the degree of histological lesions, the presence of hypertension and serum creatinine level. Interestingly, patients with the highest urinary IL-6/EGF ratio showed a worse evolution in a three year follow-up. In conclusion, our data show that: (1) renal IL-6 and EGF expression are strictly correlated to the degree of tubulointerstitial damage; and (2) urinary IL-6/EGF ratio might be a valuable prognostic marker for the progression of the renal damage in IgAN.