Hypertension associated with increased renin concentrations in nephroblastoma

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Abstract

An infant with severe hypertension who had a nephroblastoma which was secreting active renin is described. Nephroblastoma must be included in the differential diagnosis of hypertension associated with increased renin concentrations, even in the absence of an abdominal mass.

Hypertension has been known to be associated with nephroblastoma since it was first reported in 1937 by Pincoffs and Bradley.¹ The incidence of hypertension has been reported as high as 60% in some series.² This was commonly thought to be due to catecholamine production. Recently, however, several cases of nephroblastoma have been reported with raised renin concentrations. This excess renin production may be from normal renal tissue as a consequence of distorted renal vasculature by tumour compression or it may be from the tumour itself. We report a case of nephroblastoma with severe hypertension with raised renin concentrations where tumour immunohistochemistry demonstrated perivascular renin containing cells.

Case report

A 10 month old boy presented with a two week history of malaise and anorexia. On examination he was irritable and flushed, and noted to be severely hypertensive with a blood pressure of 250/194 mm Hg. His pulse was 100/minute with no radial-femoral difference. A large irregular left sided abdominal mass was palpated. Biochemical analysis showed a sodium concentration of 131 mmol/l, potassium of 3.7 mmol/l, and urea of 9.5 mmol/l. An intravenous pyelogram and computed tomogram confirmed this mass to be arising from the left kidney. Hydroxymethyl mandelic acid and vanillyl mandelic acid markers for neuroblastoma were 16 and 24 μ mol/mmol creatinine respectively (normal). Blood was also taken to measure renin concentrations.

Initial attempts at control of blood pressure with intravenous labetalol and hydralazine were unsuccessful, and so nine days after admission laparotomy was performed. Captopril, an acetyl coenzyme inhibitor, was given at induction with a good fall in blood pressure. A large nephroblastoma extending 5 cm down the ureter but with no macroscopic capsule invasion was removed. The right kidney felt normal.

Postoperatively the boy made a good recovery. His blood pressure fell to normal by the second postoperative day and his antihyperten-

sive medication was stopped. The patient was given vincristine and actinomycin D (0.025 mg/kg of each) for 26 weeks according to the United Kingdom Children's Cancer Study Group protocol and is well one year postoperatively.

Methods and results

RENIN ASSAY

Preoperatively and one week postoperatively, blood was taken for measurement of renin concentration. Active and total renin were measured by the method of Millar *et al.*³ For active renin, 35 μ l of plasma was incubated at 37°C in duplicate with excess ox renin substrate and antibody to angiotensin 1 at pH 6.9. The rate of generation of angiotensin 1 was measured by radioimmunoassay and the results calibrated against a preparation of international standard renin.⁴ For total renin, the plasma was treated with trypsin in order to convert the prorenin to renin. At very high concentrations of renin, this can lead to a slightly low figure for total renin because of renin degradation by trypsin and problems with the dilutional technique. Inactive renin was calculated as total renin-active renin.

Total renin and particularly active renin concentrations were found to be grossly raised preoperatively at 13 385 μ U/ml and 9 674 μ U/ml respectively (normal 50 μ U/ml and 200 μ U/ml). Postoperatively these fell to 8 and 55 μ U/ml.

HISTOLOGY

The specimen weighed 635 g and measured 17 $\times$ 10 $\times$ 9 cm. The tumour was a moderately well differentiated nephroblastoma predominantly blastemal in type but with prominent glomeruloid structures and some areas of increased tubular differentiation, and was classified as stage 2 favourable histology.

Using an antibody to pure renin and a peroxidase-antiperoxidase technique,⁵ most of the cells containing immunoreactive renin were present in a perivascular position in the blastemal areas as previously described.⁵ Within the glomeruloid structures there were some renin containing cells in a mesangial distribution. These cells contained granules that stained positively for renin and their appearance suggested that they were renin secreting cells.

Discussion

In the case reported, active renin was raised 50-fold preoperatively and fell postoperatively to

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Accepted 22 October 1990

Cases of nephroblastoma associated with hypertension and raised renin concentration

Author	Age	Sex	Side (R, right; L, left)	Blood pressure (mm Hg)	Renin concentration ($\mu\text{U/ml}$)	
					Preoperative	Postoperative
Spergel <i>et al</i> ⁶	5 months	F	R	210/160	14.5	2.8
Mitchell <i>et al</i> ⁷	23 months	F	R	260/200	12.3	0.66
Marosvari <i>et al</i> ⁸	18 months	M	L	160/120	15.0	7.0
Sukarochano <i>et al</i> ²	4.5 years	M	L	200/110	16 000*	220*
Sukarochano <i>et al</i> ²	5 years	M	R	162/128	810	
Ganguly <i>et al</i> ⁹	4 years	M	R	200/140	10.1	0.09
Cobb and Vaughan ¹⁰	27 months	M	R	210/140	Raised	ND
Sheth <i>et al</i> ¹¹	16 months	M	R	200/120	39.5	1.6
Luciani <i>et al</i> ¹²	3 years	M	L	200/120	51.0	1.1
Luciani <i>et al</i> ¹²	4 years	M	L	210/140	3.4	0.47
Spahr <i>et al</i> ¹³	4 years	M	L	170/120	8.8	0.35
Stine <i>et al</i> ¹⁴	9 months	M	L+R	162/110	51.9	0.77
Suthers <i>et al</i> ¹⁵	2 years	M	L	220/148	5.2	0.33
Yokomori <i>et al</i> ¹⁶	9 months	F	L+R	140/90	99.0	0.05
Khan <i>et al</i> (current case)	10 months	M	L	250/194	268	0.16

*No normal values stated, units are ng. ND, not done.

within normal limits as did the blood pressure. The inactive form was also raised but not to the same degree. The renin was found to be arising from the tumour.

The first association of nephroblastoma with raised serum renin concentrations was in 1969.⁶ The case reported was a 5.5 month old child with a blood pressure of 210/160 mm Hg associated with hypokalaemia, abnormal glucose tolerance, and increased renin concentrations. Mitchell *et al* demonstrated raised renin concentrations in tumour tissue as well as serum in a 23 month old child with hypokalaemia and a blood pressure of 260/200 mm Hg.⁷ This was thought to be evidence of abnormal renin production from the tumour rather than as a result of an ischaemic stimulus to the renin angiotensin system in the rest of the kidney. Since that report of Mitchell *et al* there have been 12 other reports of nephroblastoma associated with hypertension and increased renin concentrations (table). There is a sex ratio of four males to one female and the average age is 3 years. The time taken for the blood pressure to fall in most cases was between one and three weeks after nephrectomy. This time appears unrelated to the presence or subsequent development of metastases.

There have been a number of cases of nephroblastoma with increased concentrations of renin who were normotensive. Renin production was looked at in eight children with nephroblastoma by Voute *et al*.¹⁷ Blood pressure was normal in all eight while the serum renin concentration was found to be raised. In the five studied postoperatively, there was noted to be a fall in serum renin after nephrectomy. Day *et al* found renin in tissue from nephroblastoma with a much greater molecular weight than normal plasma and kidney renin.¹⁸ They suggested the existence of an inactive pro-hormone and this inactive form of renin could account for the large number of cases of nephroblastoma which are not associated with hypertension. Carachi *et al* looked prospectively at eight children with nephroblastoma measuring both active and inactive renin.¹⁹ In seven of these cases there was found to be a raised concentration of serum renin. However, this increased amount was seen to comprise mainly the inactive form. Only one child was hypertensive.

Nephroblastoma should always be considered

as part of the differential diagnosis for hypertension in the young. Renin concentrations should be checked and if found to be raised, a careful search should be made for a nephroblastoma even in the absence of an abdominal mass—particularly where there is no evidence of renal parenchymal disease.

We would like to thank Mr AHB Fyfe for permission to present this case. Thanks also to the departments of pathology, radiology, and medical illustration in the Royal Hospital for Sick Children, Glasgow.

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