Pediatr Nephrol (2012) 27:1037–1040
DOI 10.1007/s00467-012-2123-y

BRIEF REPORT

Hyponatremic hypertensive syndrome in pediatric patients: is it really so rare?

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Received: 17 September 2011 / Revised: 23 December 2011 / Accepted: 23 January 2012 / Published online: 26 February 2012

Abstract
Background Hyponatremic hypertensive syndrome (HHS) is characterized by unilateral renal artery stenosis with secondary hypertension and glomerular and tubular dysfunction due to hyperfiltration and activation of the renin–angiotensin system (RAS).
Case-diagnosis/treatment We describe four children with HHS. All presented with polyuria and polydipsia, electrolyte disturbances, metabolic alkalosis, variable tubular dysfunction, and nephrotic range proteinuria along with hypertension. Interestingly, in one patient, glomerular and tubular abnormalities preceded the development of hypertension. All symptoms resolved after the underlying renal ischemia was corrected by percutaneous angioplasty.
Conclusion Hyponatremic hypertensive syndrome may be more common in children than previously thought. Clinicians should be alert of the signs and symptoms because cure is possible with timely diagnosis and treatment.

Keywords Hypertension · Renal artery stenosis · Hyponatremic hypertensive syndrome · Renin-angiotensin system · Proteinuria · Tubular dysfunction

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Introduction

Hyponatremic hypertensive syndrome (HHS) is characterized by malignant hypertension, hyponatremia, and hypochloremia secondary to unilateral renal artery stenosis or occlusion. The combination of symptoms was first reported in 1950 by Hilden [1] in a series of five adult patients; the term HHS was introduced 15 years later by the Medical Research Council Blood Pressure Unit of Glasgow [1–3]. In 1999, Agarwal et al. [4] studied a series of 32 adults with renovascular hypertension associated with HHS. All presented with severe hypertension, thirst, polyuria, weight loss, confusion, and hyponatremia. HHS has been described in children as well [5–13], starting with the report of Blanc et al. [5] in 1991. Laboratory findings of elevated plasma levels of renin in most cases suggest that the stimulation of renin release from the ischemic kidney plays an important pathophysiologic role. Activation of the renin–angiotensin system (RAS) causes secondary hyperfiltration, pressure diuresis, and sodium loss from the contralateral, non-stenotic kidney. Renal handling of other solutes is also affected by this hyperfiltration state, as reflected by findings of hypokalemia, alkalosis, hypercalciuria, glycosuria, and proteinuria, sometimes within the nephrotic range [2, 4, 8, 10]. Several authors reported reversible cortical hyperechogenicity of the

nonstenotic kidney, probably a consequence of hyperfiltration and tubulointerstitial damage [10, 14].

The aim of this report is to describe our experience with HHS in four pediatric patients.

Case reports

Among all children diagnosed with renovascular hypertension at our tertiary pediatric medical center in the last 5 years, four (28%) were found to have HHS. The clinical and laboratory data of the first patient are described in detail below; the findings for the other three are summarized in Table 1.

Case 1 A previously healthy 2.9-year-old girl was hospitalized with loss of appetite, vomiting, and presyncope. Physical examination revealed no abnormalities. Blood pressure measured 90/42 mmHg. Blood test results were as follows: creatinine, 0.26 mg/dL; potassium, 3 mEq/L; sodium, 129 mEq/L; glucose, 43 g/dL; bicarbonate, 17 mEq/L. Urinalysis revealed protein at 150 mg/dL; urine collection, proteinuria of 700 mg/24 h (>40 mg/h/m^2). On the post-discharge tests after treatment with rehydration, creatinine was 0.29 mg/dL, potassium 3.7 mEq/L, and bicarbonate 27 mEq/L. Urine collection revealed polyuria of 1,250–1,500 cc/day, proteinuria of 240–480 mg/day, mostly albuminuria, hypercalciuria 6.7–11.6 mg/kg/day, and hyperuricosuria of 900 mg/day/1.73 m^2. Renal sonography showed cortical hyperechogenicity of the right kidney. The dimercaptosuccinic acid (DMSA) renoscan revealed that the right kidney contributed 60% of global function, with small areas of abnormal uptake.

The patient was admitted to the Intensive Care Unit when her blood pressure on ambulatory follow-up rose to 180/140 mmHg, although she remained asymptomatic. During hospitalization, the blood pressure levels rose further to 215/156 mmHg. The echocardiogram and fundoscopic examination were normal. Treatment with intravenous labetalol followed by a combination of oral beta blocker, angiotensin-converting enzyme inhibitor, and calcium-channel blocker

Table 1 Clinical, laboratory, and radiologic characteristics of patients with hyponatremic hypertension syndrome

	Patient 1	Patient 2	Patient 3	Patient 4
Age at presentation (months)	33	27	24	18
Sex	Female	Male	Male	Female
Symptoms at presentation	Vomiting, loss of appetite, presyncope, polydipsia, polyuria	Weakness, weight loss, polydipsia	Restlessness, vomiting, polyuria	Vomiting, dehydration, lethargy , circulatory collapse
Blood pressure at presentation (mmHg)	90/42→ 215/156	142/92	220/150	220/140
Fundoscopy	Normal	Normal	Papilledema	Normal
Echocardiography	Normal	Mild LVH	Severe LVH	LVH
Creatinine (mg/dL)	0.26	0.51	0.42	0.4
Sodium (mEq/L)	129	122	125	135
Potassium (mEq/L)	3	3.9	3.2	2.8
Bicarbonate (mEq/L)	27	25.9	27.2	30
Urinary protein excretion	0.7 g/day	3.2 g/day	5.3 g/day	Protein/Cr 2.1
Urinary calcium excretion	11.6 mg/kg/day	Ca/Cr 1.5	8.7 mg/kg/day	Ca/Cr 1.1
Urinary uric acid excretion	900 mg/day/1.73 m^2	FEUA 39%	1300 mg/day/ 1.73 m^2	FEUA 25%
Renin	Low	No data	Elevated	No data
Aldosterone	Slightly elevated	Highly elevated	Elevated	No data
Renal sonography	Hyperechogenicity of Rt kidney	Normal	Small Lt kidney, normal echogenicity	Small Rt kidney, normal echogenicity
DTPA scan with captopril	Inconclusive	Suggestive of Rt renal artery stenosis	Suggestive of Lt renal artery stenosis	Suggestive of Rt renal artery stenosis
Renal angiography	Lt upper lobe accessory artery stenosis—90%	99% stenosis of Rt renal artery	Severe obstruction of Lt renal artery	Severe obstruction of Rt renal artery
PTA	Successful	Successful	Successful	+Stent insertion partially successful
Blood pressure, blood and urinary tests after PTA	Normal	Normal	Normal	Normal

DTPA, 99m technicium diethylene triamine pentacetic acid; PTA, percutaneous transmural angioplasty; Rt, right; Lt, left; LVH, Left ventricular hypertrophy; Ca, calcium; Cr, creatinine; FEUA, fractional excretion of uric acid

led to gradual—but only partial—blood-pressure control. Renin was low at 0.84 ng/mL/h, and aldosterone was slightly elevated at 440 pmol/L (on labetalol treatment). The findings on the Doppler examination of the renal artery and diethylenetriamine pentaacetic acid (DTPA) renoscan with captopril were inconclusive. Renal arteriography revealed an aberrant accessory left renal artery supplying the upper pole of the kidney with 90% stenosis. Following cutting balloon (3/20 mm, BSC) dilatation, all parameters normalized.

Discussion

Renovascular hypertension is responsible for 5–25% of cases of secondary hypertension in children, and fibromuscular dysplasia accounts for up to 60% of cases [9, 10]. Renal artery stenosis may be due to external compression [5]. Although initially considered a rare condition, HHS has been identified in approximately 16% of adults with unilateral renal artery stenosis [4, 10]. Data on the pediatric population are still sparse [5–11]. In an editorial commentary, Nicholls [2] suggested that HHS may be underdiagnosed in children and probably more common than previously thought. Our experience supports this assumption. The four children with HSS described here represent 28% of all children diagnosed and treated for renovascular hypertension at our tertiary hospital during the last 5 years.

Presenting symptoms of HHS include weight loss, polyuria, polydipsia, enuresis, weakness, headache, clouding of consciousness, and various neurological and behavioral changes [1–5, 14, 15]. In the first two patients described here, symptoms of polyuria, polydypsia, and weight loss were very conspicuous, whereas in the last two patients, neurological symptoms (restlessness, vomiting, and papilledema) were more prominent.

Laboratory findings in patients with HHS include hyponatremia, hypokalemia, hypochloremic alkalosis, and proteinuria, sometimes in the nephrotic range [2, 8]. This was true in our patients as well. Hypercalciuria and glycosuria have been less frequently reported [2, 8]. All of our patients had marked hypercalciuria; none had glycosuria.

Renin and aldosterone levels are usually elevated in HHS. Two of our patients (Cases 2, 3) had an elevated aldosterone level, one (Case 3) had elevated levels of both renin and aldosterone, and one (Case 1) had a low renin level and a slightly elevated aldosterone level, but these were measured during labetalol treatment.

The pathophysiologic mechanism of HHS is renin secretion induced by renal ischemia leading to high circulatory levels of angiotensin II, and aldosterone secretion from the adrenal glomerulosa leading to blood volume expansion, increased blood pressure, and potassium depletion. Spontaneous diuresis through the contralateral kidney ensues, with correction of the hypervolemia. This "aldosterone escape" phenomenon is apparently due to the decrease in sodium reabsorption caused by the increased secretion of atrial natriuretic peptide and elevated blood pressure ("pressure natriuresis"). It does not, however, represent aldosterone resistance, since the urinary potassium loss continues and the cortical collecting tubule remains responsive to aldosterone. The consequent volume depletion could lead to postural hypotension and a further release of renin from the kidneys. Together with the high level of angiotensin II, the volume depletion increases thirst and the release of antidiuretic hormone. All of these changes, along with the sodium depletion secondary to pressure natriuresis, cause hyponatremia. The pressure-induced hyperfiltration and natriuresis might be responsible for the hypercalciuria and hyperuricosuria, while the proteinuria may be secondary to hyperfiltration due to the proteinuric effect of angiotensin II and, probably, atrial natriuretic peptide [2, 9, 10, 13–15]. Accordingly, for HHS to occur, the stenosis of the renal artery must be unilateral, and perfusion and function of the contralateral kidney must be normal [9, 13].

Patients 2, 3, and 4 presented with severe hypertension (142/92, 220/150 and 220/140 mmHg, respectively), as expected in HHS. However, Patient 1 had normal blood pressure (90/42 mmHg) at presentation. Subsequent evaluation revealed that she already had hypokalemia, alkalosis, nephrotic range proteinuria, hypercalciuria, and hyperuricosuria. Only months later did her blood pressure gradually rise, and ultimately severe hypertension and HHS did develop. Our literature search did not yield any other reported case in which the characteristic glomerular and tubular dysfunction of HHS preceded the occurrence of overt hypertension. The atypical course in this patient may be attributable to the 90% stenosis of her aberrant accessory left renal artery, which supplied the upper pole of the kidney. This vascular anomaly could have been associated with over-intensified hyperfiltration and pressure natriuresis via the contralateral normal kidney and the normal part of the ipsilateral kidney (supplied by the main left renal artery), leading first to glomerular and tubular dysfunction and a state of dehydration that might overcome the pressor activity of angiotensin II. When decompensation of this mechanism occurred, fluid and sodium retention ensued and together with augmentation of angiotensin pressor activity led to gradual elevation of blood pressure.

Hyperechogenicity of the contralateral kidney in cases of HHS induced by unilateral renal artery stenosis has been described previously in patients with HHS [10, 12]. The assumed cause is the hypercalciuria and increased solute load caused by hyperfiltration. It is accompanied by tubular reabsorption and consequent tubulointerstitial damage probably induced by the deposition of calcium and uric acid [10, 12]. In addition to renal sonography, the DMSA renoscan can clearly identify this state. In Patient 1, the DMSA

renoscan showed an enlarged normal kidney with areas of abnormal uptake. The changes usually resolve completely with correction of the renal artery stenosis and consequent cessation of the hyperfiltration state. However, they may be irreversible if diagnosis and treatment are delayed.

The treatment of choice for children with renovascular hypertension due to fibromuscular dysplasia is percutaneous transmural angioplasty (PTA), with a reported success rate of 90–100% [9]. However, the technical success rate of PTA in children with HHS is lower [10]. Ashida et al. [9] hypothesized that HHS develops in children only when the stenosis in the affected artery is so severe that revascularization by PTA is impossible. Nevertheless, three of our patients had critical renal artery stenosis, and all were successfully revascularized by PTA. The fourth patient had restenosis following the first administration of PTA and was successfully revascularized afterward by PTA and stent insertion. Clinicians should be alert to the possibility that a finding of unexplained electrolyte abnormalities along with glomerular proteinuria in a child, in the absence of other parameters of glomerular disease or clear-cut tubulopathy, could indicate an evolving renovascular hypertension which warrants prompt close blood pressure monitoring. Asymmetric findings on renal sonography should further raise suspicions. Our report is noteworthy given the importance of early diagnosis and treatment. In all our patients, as in other reports of HHS, symptoms and laboratory findings were completely reversed. Further studies to determine the true incidence of HHS in children are warranted.

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