

Pediatric hyponatremic hypertensive syndrome

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Hyponatremic hypertensive syndrome is an important complication of severe arterial hypertension with the potential for significant morbidity and mortality. It is recognized by the association of the clinical signs and symptoms of hyponatremia and hypertension accompanied by inappropriately high urinary output and electrolyte losses. According to the available literature there are data for only 20 children with the syndrome; 15 of which had underlying renovascular disease, most commonly due to fibromuscular dysplasia of renal arteries. Stimulation of the renin–angiotensin system from the ischemic kidney seems to play an essential role in the pathogenesis of hyponatremic hypertensive syndrome. The outcome if untreated is poor. However, if recognized in time and appropriately treated, it can sometimes be cured. The aim of this paper is to raise awareness of this hypertensive complication in children to insure that it is appropriately investigated and treated.

Traditionally, arterial hypertension has been considered a hypervolemic state with increased total body sodium. The association of arterial hypertension with hyponatremic dehydration is not widely known. The first descriptions of severe hypertension associated with poliuria, hypovolemia and hyponatremia were reported in the early 1950s [1–4]. In 1965, Brown and colleagues named the combination of hyponatremia caused by renal sodium loss and severe hypertension the hyponatremic hypertensive syndrome (HHS) [5]. Following this, HHS has been reported infrequently, mainly in adult patients [6–14]. Pediatric data regarding the HHS is still very limited [15–20].

The most common cause of arterial hypertension in HHS is renovascular disease. The pathophysiology of this phenomenon is complex and not yet fully understood. Treatment of underlying hypertensive disorder is crucial for the management of HHS, but initially, rehydration with sodium supplementation is necessary to correct water and electrolyte abnormalities. The development of potent antihypertensive agents, especially those that suppress the activity of the renin–angiotensin system (RAS) and/or percutaneous transluminal angioplasty or surgical revascularization, have resulted in significant reductions in morbidity and mortality due to the HHS.

This review will discuss the epidemiology, pathophysiology, clinical presentation, treatment and outcome of HHS focusing on the pediatric aspect. The purpose of the article is to raise awareness of HHS in children to insure that it is appropriately investigated and treated.

Epidemiology

The incidence of HHS among hypertensive patients is not readily apparent from the literature. According to McAreavey and colleagues, who noted hyponatremia in six out of 35 adult patients with renovascular hypertension [7], and Agarwal and colleagues who identified 32 mature patients with hypertension and hyponatremic dehydration in a city population of 350,000 [14], HHS is not uncommon, but is a rather under-recognized hypertensive disorder in adult patients with renal ischemia. It is to be expected that HHS is less frequent in the pediatric population than the adult, as the overall incidence of arterial hypertension is much lower in children. The report of the 4th Task Force on Blood Pressure Control in Children indicates that 1% of children will have hypertension confirmed on repeated measurements [21], while in middle-aged adults (45–54 years of age) the incidence of hypertension varied from 26.2 to 58.3% [22]. 'Severe' hypertension in children is defined as systolic and/or diastolic values greater than the 99th percentile for age, gender, and height, and/or the presence of symptomatic target organ disease [21]. Prevalence in children is approximately 0.1%, and is mainly as a consequence of renal disease [23,24]. The reported incidence of renovascular disease in hypertensive children is 3 to 10% compared with a 1% incidence in adults [25,26]. In contrast to adult patients where renovascular disease is most commonly due to atherosclerosis [26], 75 to 95% of children with renovascular disease have some form of arterial dysplasia [25].

Keywords: ACEI, angiotensin, children, hyponatremia, renal artery stenosis, renin, severe hypertension

The name 'HHS' implies that hyponatremia is necessary for the diagnosis, otherwise the condition would be simply hypertension. The high incidence of hyponatremia (30%) found by Skalina and colleagues in hypertensive newborns suggests that HHS could have been underestimated in the youngest infants [27]. According to the available literature, there is data for only 20 children with HHS; three of these have been reported recently [20,28,29].

At the University Children's Hospital of Belgrade, which is the referral center covering about 1.4 million children (aged below 18 years) in Serbia, no one case of HHS had been diagnosed until 2000. From that date onwards, four cases of HHS in hypertensive children have been recognized; one patient in 2000 [18], a second in 2002 [19], and an additional two in 2004 (Table 1). Accordingly, one might speculate that HHS is not as rare in

children as might be concluded based on scarce reports in that literature. Rather however, it is the case that it has been under-reported.

The majority of reported adults with HHS were elderly asthenic females (mean age of 65.1 years) and the underlying renal artery pathology was atherosclerosis [14]. Conversely, pediatric HHS has been most frequently reported in the youngest children, more frequently in boys than in girls, and the fibromuscular dysplasia of renal arteries has been the most common underlying cause (Table 1). Thus, HHS is prevalent in the youngest boys with congenital renovascular defects and elderly females with acquired, severe atherosclerotic disorder.

Pathophysiology

The most important factor leading to the development of HHS is a severe, arterial hypertension. The mechanism of hypertension-induced natriuresis, poliuria and proteinuria in HHS is still

Table 1. Cases of pediatric hyponatremic hypertensive syndrome

Authors	No. of cases	Etiology	The main presenting signs and symptoms	Treatment	Outcome	Refs
Rosendahl <i>et al.</i> (1980)	1	Left renal artery thrombosis	Severe hyponatremic dehydration	Symptomatic	Fatal	[15]
Blanc <i>et al.</i> (1991)	1	Right RAS + multiple arterial lesions	Anorexia Dehydration Congestive heart failure	Right nephrectomy	BP normal without therapy	[36]
Kaneko <i>et al.</i> (1994)	1	Left RAS	Polydipsia Dehydration Mild somnolence	PTA	BP and all other abnormalities normalized	[16]
Misjani <i>et al.</i> (1994)	1	Renin-producing leiomyosarcoma	Proteinuria Polyuria Hypertension	Removal of the leiomyosarcoma	Relapse	[11]
Castello <i>et al.</i> (1996)	2	Unilateral RAS	Poliuria Polydipsia Dehydration	Revascularization	BP and all other abnormalities normalized	[37]
Gouyon <i>et al.</i> (1997)	3	One: left RAS two: bronchopulmonary dysplasia	Dehydration Poliuria	Pharmacologic	BP normalized or improved	[35]
Daftary <i>et al.</i> (1996)	1	Renal microthrombi	Convulsions	Pharmacologic	Favourable	[48]
Dahlem <i>et al.</i> (2000)	1	Left RAS	Behavioural abnormalities	Nephrectomy	BP normal without drugs 12 months after nephrectomy	[17]
Peco-Antic <i>et al.</i> (2000)	1	Right kidney scarring Hyper-reflexive bladder	Altered level of consciousness Seizures Vomiting Dehydration	Pharmacologic	BP normal with angiotensin-converting enzyme inhibitor	[18]

BP: blood pressure; PTA: Percutaneous transluminal angioplasty; RAS: Renin-angiotensin system; [§]Not reported.

Table 1. Cases of pediatric hyponatremic hypertensive syndrome (cont.)

Lang <i>et al.</i> (2003)	1	Left RAS	Nephrotic syndrome Failure to thrive	Nephrectomy	BP normalized	[49]
Peco-Antic <i>et al.</i> (2003)	1	Bilateral RAS neurofibromatosis	Facial nerve paralysis Vomiting Dehydration	PTA failed, auto-transplantation successful	BP normal with labetalol and nifedipine	[19]
Bourchier (2003)	2	Unilateral renal ischemia (dislodged aortic thrombus into renal artery)	Hyponatremia Hypertension Atrophy of ischemic kidney	Nephrectomy in one, pharmacologic in other	BP normalized	[50]
Cauchat <i>et al.</i> (2004)	1	Right RAS	Tachypnea Nephrotic range proteinuria	Pharmacologic	BP normalized with enalapril	[28]
Dixit <i>et al.</i> (2004)	1	Left renal stenosis	Drowsiness Seizures Pinpoint pupils	The surgical revascularization	BP normal with labetalol and amlodipine	[20]
Peco-Antic ⁵ (2004)	2	One polycystic kidney disease and idiopathic atrial dilatation One polyarteritis nodosa	Hypertension Severe hyponatremia Dehydration Heart failure Signs of systemic inflammation Hypertension Hyponatremia Polyuria Dehydration Proteinuria	Pharmacologic Pharmacologic	In both patients BP and all other abnormalities normalized	
Trivelli <i>et al.</i> (2005)	2	Left RAS	Polydipsia Dehydration	The surgical revascularization	BP normalized	[29]

BP: blood pressure; PTA: Percutaneous transluminal angioplasty; RAS: Renin-angiotensin system; ⁵Not reported.

unclear. Most probably it is the consequence of a number of different interlinked factors, rather than a single one. Stimulation of renin release from the ischemic kidney has a central role. The crucial pathogenetic activity of angiotensin in the glomerular and tubular defects of HHS has been confirmed in clinical and experimental studies. In a case report of a patient with HHS and renin-producing leiomyosarcoma, enalapril treatment, as well as the removal of leiomyosarcoma, regulated hypertension, electrolyte abnormalities and reduced proteinuria; the relapse of neoplastic disorder with consequent increase of plasma renin activity led to a fully blown clinical picture of HHS [11]. In animals, infusion of high doses of angiotensin increases sodium excretion by the normal kidney, thus exceeding the effect of aldosterone on tubular sodium reabsorption [30]. There is no doubt that we are still to learn the exact pathophysiological mechanisms of a paradoxical hypernatremia and polyuria that persist in secondary hyperaldosteronism of HHS. The intrinsic renal autoregulation mechanism is adjusted mainly by angiotensin II and the sympathetic nervous

system. At the level of the renal glomerulus, angiotensin II can be expected to cause vasoconstriction of postglomerular efferent to a much greater degree than preglomerular afferent arterioles, thus increasing glomerular capillary pressure and glomerular filtration. At the tubular level, angiotensin II indirectly, through its effect on aldosterone synthesis, promotes collecting duct sodium reabsorption, while its effect on proximal tubule sodium reabsorption is direct, biphasic and dose dependent. At physiologic concentrations (10^{-10} to 10^{-12} M), angiotensin II stimulates proximal sodium and water reabsorption, but at elevated concentrations (10^{-6} to 10^{-7} M) it can inhibit reabsorption [31]. What may be found in HHS is that the activated RAS leads to a pressure natriuresis via the normal kidney while elevated concentrations of angiotensin II can inhibit proximal tubule sodium and water reabsorption. These effects result in polyuria and urinary sodium loss. The proximal tubule possesses an intrarenal 'self-contained' RAS [32]. Therefore, plasma renin activity may not always be a reliable marker of

the activation of intrarenal RAS [29,32]. The effect of endogenously produced angiotensin on proximal tubule transport is higher after volume contraction than after volume expansion [31], which may be an additional factor in HHS for a vicious circle to be set up: severe hypertension – renal ischemia – stimulation of renal renin release – angiotensin II production – ‘pressure natriuresis’ and inhibited proximal tubular sodium and water reabsorption – volume contraction – activated sympathetic system – increased production and effect of angiotensin II – aggravation of hypertension.

High-molecular weight proteinuria of HHS, that is sometimes in the nephrotic range [28], is probably for the mostpart related to the impairment of glomerular membrane permselectivity due to the influence of angiotensin. Indirect evidence for an angiotensin-induced defect in intrinsic membrane selective properties regardless of its effects on hemodynamic changes was obtained in a study of glomerular size-selective properties before and 6 months after enalapril therapy in a patient with HHS [10]. Treatment with enalapril normalized blood pressure, corrected electrolyte abnormalities and reduced proteinuria. Enalapril effectively restored glomerular size-selective function, reducing dimensions of membrane pores, independently of its effect on renal hemodynamics [10].

On the basis of the results of the experimental studies in animals it is speculated that increasing the renal perfusion and interstitial hydrostatic pressures are responsible for a decrease in tubular water and sodium reabsorption [33,34]. Pressure natriuresis is a suspected contribution to hyponatremic dehydration especially in infants with severe hypertension due to renal and non-renal causes [35]. It has been demonstrated in the case of unilateral renal ischemia that the untouched, intact contralateral kidney, submitted to high pressure diuresis is responsible for the negative sodium and water balance and its consequence [36–38]. After improving blood pressure control, urinary excretion of sodium and potassium of the contralateral kidney normalized [38]. In most pediatric cases of HHS, renal ischemia was unilateral due to renal artery stenosis. In many of these patients, increased peripheral plasma renin activity and increased plasma aldosterone were documented (Table 1). Some of the patients with HHS had bilateral renal ischemic disease, but ischemia was critical on one kidney, resulting in the intense stimulation of renin from the juxtaglomerular apparatus, whereas perfusion

pressure to the contralateral remained relatively high, thereby facilitating a pressure natriuresis leading to a volume-depleted state and hyponatremia. Plasma renin levels usually correlated inversely with plasma sodium concentrations. Renin secretion is also stimulated by plasma potassium deficiency, resulting in a vicious cycle, while only moderately decreasing aldosterone secretion. Prolonged hypokaliemia contributes to polyuria due to vasopressin-resistant concentrating ability [39].

In addition to well-recognized renal water, sodium, potassium and chloride reabsorption defects, hypercalciuria and glycosuria were recently reported in two young children with HHS [29]. Hypercalciuria lasted for several months after the normalization of other urinary electrolyte loss and proteinuria, probably reflecting the need to restore enough enzyme for tubular reabsorption of calcium [29]. Taken together, these characteristics indicate that more extensive than expected renal (glomerular, proximal and distal convolute tubular) functional defects may be found in HHS.

Clinical presentation

Patient data are listed in Table 1. In young children, HHS represented an emergency in which hyponatremia is often predominant and hypertension is only casually detected. The neurological manifestations of hyponatremia are the main presenting symptoms. They ranged from mild, such as headache, nausea, emesis and weakness which could be easily overlooked, to more severe such as respiratory depression, seizures, coma and respiratory arrest. Psychiatric signs have been observed, such as bizarre behavior around recent onset [17]. Other manifestations of ‘hyponatremic, hypoxic encephalopathy’ appeared less frequently. These are bradycardia, hypothermia, focal or generalized weakness, ataxia, Babinski sign, depression and cognitive impairment. Although, generally accepted as 130 mmol/l or less, the degree of hyponatremia determined by the serum sodium level does not always correlate in a linear fashion to the presence of symptomatology.

The critical factor for determining the development of clinical symptomatology of hyponatremia is the rate of decrease in serum sodium levels. Acute hyponatremia, defined as a decrease of plasma sodium concentrations to 120–125 mEq/l or less within 48 h, may cause cerebral edema and brain stem herniation [40]. This is a result of hypotonicity, which causes

water to equilibrate across cell membranes as it moves down an osmotic gradient from extracellular fluid into cells. An abrupt fall in serum osmolarity of 5 mEq/l in the presence of an intact blood–brain barrier produces a decrease in the osmotic pressure difference between the capillary lumen and the brain interstitium of 95 mmHg, favoring water accumulation in brain parenchyma [41]. An increase in brain volume of 5% can result in neurologic problems [42]. Histopathologic findings in patients with acute hyponatremia and respiratory arrest demonstrate characteristics of cerebral hypoxia. Children are at a greater risk for hyponatremic hypoxic encephalopathy than adults because their brains have a large intracellular fluid volume per unit of total skull volume, and more than likely have a decreased capacity for cerebral adaptation to low osmolarity [43].

The gradual development of hyponatremia may not result in neurologic dysfunction due to adaptive osmoregulatory mechanisms that allow the brain to normalize its water content when subjected to a changing osmolar environment. Morbidity can result from rapid correction of asymptomatic hyponatremia, manifested as neurologic deterioration by a decreasing level of consciousness, behavioral changes without focal findings, a ‘locked-in syndrome’, spastic quadriplegia, pseudobulbar palsy, and imaging (on computed tomography [CT], magnetic resonance imaging [MRI]) or postmortem findings of demyelinating lesions through the brain [42]. Sterns and colleagues proposed that these lesions resulted from CNS dehydration secondary to a rapid rise in serum osmolarity in the presence of normal or reduced brain water content [44]. Hypokalemia may predispose to demyelination lesions due to a decreased availability of potassium in the brain [42].

In children suffering from HHS, neurologic symptoms related to acute hyponatremia or to a rapid correction of chronic hyponatremia may be associated and/or confused with neurologic symptoms of hypertensive encephalopathy due to the similarity in clinical features. The most common symptoms of hypertensive encephalopathy include headache, nausea, vomiting, visual blurring, impaired cognitive function and generalized seizures. Hypertensive encephalopathy is likely to arise from the loss of autoregulation in cerebral vessels due to an abrupt rise in blood pressure. The result is cerebral vasodilatation, hyperperfusion, breakdown of the blood–brain barrier, plasma exudation

and focal cerebral edema. As blood pressure is lowered, fluid extravasations decrease and cerebral autoregulation returns.

Apart from the clinical signs and symptoms of hyponatremia and hypertension, HHS is also characterized by moderate-to-severe dehydration accompanied by body weight loss and inappropriately high urinary output [16,18]. Severe dehydration was the sole clinical symptom in hypertensive preterm infants reported by Guyon and colleagues [35]. It was related to marked polyuria and natriuresis levels of up to 575 ml/kg per day and 73 mEq/kg per day, respectively [35]. Intravenous water and solute infusion, although very often required, were not able to normalize dehydration and electrolyte loss without blood pressure regulation.

Diagnostic strategy

Differential diagnosis of pediatric HHS include primary neurologic disease, such as intracranial hemorrhage or malignancy, inappropriate secretion of antidiuretic hormone, endocrine deficiency such as diabetes insipidus and Addison’s disease, gastrointestinal losses, psychiatric illness, recent drug (diuretic) ingestions and renal disorders known as ‘salt losing’ nephropathy and chronic renal failure. The combination of hypokalemia with hyponatremic hypovolemia and hypertension is a useful clue to HHS. Hypokalemia may be severe with symptoms mimicking gastrointestinal disease or renal tubular disorder. The combination of hypokalemia with hyponatremic hypovolemia and hypertension is a useful clue to HHS.

As there are many causes of hyponatremia and treatment differs accordingly, a logical and efficient approach to the evaluation and management of patients with hyponatremia is imperative. The identification of hyponatremia must be followed by a clinical assessment of the patient, beginning with a targeted history to elicit the symptoms and duration of hyponatremia and to exclude its important causes. Next, physical examination must be carried out, including blood and urine examinations. Useful investigative aids include measurement of plasma osmolarity and urinary electrolyte concentrations, especially sodium concentrations. Plasma osmolarity testing places the patient into one of three categories, normal, high or low plasma osmolarity. Urinary sodium concentration testing is used to refine the diagnosis in patients who have a low plasma osmolarity. Hypo-osmolar dehydration associated with high urinary output and with excess renal

sodium concentration (>30 mmol/l) in severe hypertensive patients is critical for the diagnosis of HHS. Further investigations include the determination of plasma renin activity and aldosterone level, measuring the glomerular filtration rate (GFR) or serum creatinine and proteinuria, and kidney imaging procedures. All children with HHS should be fully assessed for the possibility of a correctable renal arterial lesion. Clinical features suggesting renal artery stenosis include young children with severe hypertension who may be refractory to nonangiotensin-converting enzyme inhibitor (ACEI) regimens, fall in blood pressure and/or a decrease in GFR with ACEIs, the presence of flank or periumbilical bruits, normal renal function studies together with urinary findings not suggestive of renal parenchymal disease, and asymmetry in renal size. While angiography remains the gold standard for the diagnosis of renovascular disease, newer imaging modalities, such as gadolinium-enhanced MRI and spiral CT angiography are becoming more widely available and have the potential to provide noninvasive diagnosis [25,45].

If renovascular disease is excluded, it is necessary to continue with other examinations, such as voiding cystography and urodynamic studies in order to elucidate the primary cause of renal ischemia [18].

Treatment

Management of pediatric HHS is based on the treatment of hyponatremic dehydration plus antihypertensive therapy; the latter being most important as it halts ongoing renal water and electrolyte losses. The treatment strategy of hyponatremia should focus on the following issues:

- A careful correction of serum sodium
- Assurance of an adequate circulation
- Continued monitoring and maintenance of a safe water and electrolyte homeostasis

First, the physician must decide whether immediate treatment of hyponatremia is required. This decision is based on the presence of symptoms, degree of hyponatremia, and whether the condition is acute (arbitrarily defined as a duration of less than 48 h) or chronic. Symptomatic, acute hyponatremia with a decreased level of consciousness is the urgent problem, which needs immediate treatment. Such patients should be treated with infusion of hypertonic saline (3% saline). The infusion rate is initially adjusted to raise plasma sodium at a rate of approximately 1.0 mmol/l/h and then followed by 0.5 mmol/l/h [46]. It is discontinued when the patient becomes asymptomatic (neurologically

stable) or when patient serum sodium reaches a value of around 126 mmol/l. However, the problem of symptomatic hyponatremia in pediatric HHS is more complex due to the association of hyponatremic and hypertensive hypoxic lesions. There is a need for some correction of hyponatremia, while simultaneously avoiding the osmotic demyelinating syndrome that is irreversible. In most children with HHS, a rapid rise in serum sodium concentration is not necessary. Therapy should be directed at the normalization of arterial hypertension and treatment of the underlying etiology. In addition, there is a need for a gradual improvement of circulation and serum sodium concentrations that can usually be achieved with administration of isotonic fluids; normal saline, followed by 0.45% sodium chloride and 5% dextrose.

Antihypertensive treatment is the cornerstone of HHS treatment. Initially it consists of pharmacologic therapy as an urgent measure. Blood pressure should be reduced extremely slowly, without instituting precipitous falls, and allowing preservation of target organ function, especially CNS perfusion [24]. In general, the slow reduction in blood pressure by a third of the total desired reduction in blood pressure should be achieved within the first 12–24 h by the use of intravenous infusions of sodium nitroprusside (0.5–8.0 µg/kg/min intravenous infusion) or labetalol (0.3–1.0 mg/kg as intravenous bolus, then 0.4–3.0 mg/kg/h as continuous infusion) or nicardipine (5–10 µg/kg/min as continuous infusion), which can be titrated against the response [21]. During the following 12 h blood pressure is decreased by a second-third of the total desired reduction in blood pressure, and finally the normalization of blood pressure should be achieved after 48–72 h. Blood pressure should be monitored continuously during this process, and if an abrupt fall in blood pressure occurs, antihypertensive therapy must be decreased or stopped, while intravenous dexamethasone and rapid infusion of normal saline will help to adequately preserve critical organ perfusion. Once blood pressure is controlled, oral agents should be introduced and intravenous ones could be gradually weaned. When the patient is more stable, investigation for secondary causes should be performed, as guided by presenting clinical and laboratory findings. Specific treatment of the etiology, such as angioplasty, may be delayed until the patient has recovered from the effect of high pressure and adequate circulation with normal serum electrolytes has been stabilized [24].

Medical management

Long-term antihypertensive therapy

Due to the pathophysiologic consideration of HHS, the agents that are less likely to stimulate renin release are preferable. ACEIs (captopril, enalapril, lisinopril or ramipril) and/or angiotensin receptor blockers (ARBs; losartan or candesartan) are generally effective in reducing systemic blood pressure, but a risk of acute renal failure may be high; up to 23–38% for RAS in a solitary kidney and for a bilateral one, respectively [25]. If recognized in time and adequately treated, acute renal failure due to the blockade of the RAS is reversible [18]. Acute complications of ACEIs and/or ARBs are much lower in patients with unilateral RAS, at about 9% [25]. However, long-term use of these agents may result in chronic deterioration in renal function. Calcium channel inhibitors may be used due to their minimal effect on GFR and compensatory renin release. Labetolol and α -adrenergic blocking agents are suitable antihypertensive medication as they may suppress renin release and catecholamine effects. Salt intake should be moderate and diuretic use should be avoided.

Revascularization procedures

As hypertension caused by renovascular disease is often severe and medical therapy may be ineffective or risky, percutaneous transluminal angioplasty (PTA) or surgical revascularization

are recommended to help preserve renal function and to eliminate or reduce the need for a life-long use of antihypertensive medications. PTA should be the primary procedure, particularly when the stenosis is beyond the ostium of the renal artery. A skilled interventional radiologist may dilate vessels with an internal diameter as small as 1 mm [16,25]. In patients with ostium lesions and in syndromes with aorto-renal involvement, such as neurofibromatosis, surgery may be favoured due to a better outcome and fewer complications compared with PTA [19,25,41]. Angioplastic reconstruction or autotransplantation of one or both kidneys has resulted in cure or significant improvement of arterial hypertension in severe bilateral, or complex RAS in children with HHS [19,20,29,37]. The long-term outlook for these patients is excellent.

Nephrectomy is an alternative to revascularization when it is very complex and is associated with high operative risk, or when the kidney contributes less than 10% of renal function [17,36,49].

Outcome

The outcome for untreated HHS is poor. In adult patients, the HHS mortality rate is rather high (25%), and there is a frequent need for multiple antihypertensive therapies [14]. The mortality rate in children is lower than in adults (5.5%), and the control

Executive Summary

- Although the majority of cases of hyponatremic hypertensive syndrome (HHS) have been described in children with renal ischemia, other etiologies, such as renal dysplasia (not necessarily an ischemic lesion) and renal tumors, have been described.
- Hypertension in cases of HHS is associated with activation of the renin–angiotensin system (RAS), rather than renal ischemia *per se*. The neurologic manifestations of hyponatremia and/or hypertensive encephalopathy are the main presenting symptoms and they are not always in linear correlation with the degree of hyponatremia and/or hypertension.
- The cornerstone of management is the treatment of underlying hypertensive disease. However, correction of hyponatremic dehydration and a safe decrease in blood pressure is also essential in the emergency phase of HHS.
- Optimal antihypertensive therapy depends on the underlying condition. Revascularization, either surgically or by percutaneous transluminal angioplasty (PTA), is recommended for children with renal artery stenosis.
- Pharmacologic treatment based on angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers is the most efficient antihypertensive therapy for those with ischemic renoparenchymal disorder. It is important to emphasize that the use of ACEIs in the presence of renal artery stenosis can lead to renal shut-down that can be irreversible.
- Furthermore, extreme caution is required, as renovascular disease in children is often bilateral and involves small vessels that can only be visualized by angiography. Nephrectomy is performed if an affected kidney contributes less than 10% of the global renal function, if PTA fails and the operative risk is too high, or in the case of extensive tumorous lesions.

of blood pressure is better after PTA or revascularization than with medications. Pharmacologic management was quite disappointing in nine out of 14 children with HHS due to renovascular disease [15–17,19,20,29,36,49]. Hypertension was cured after PTA in one child [16], while revascularization was successful in four [19,20,29]. Of these, one patient had surgical revascularization of three stenotic arteries unilaterally [20]. Renal autotransplantation that was performed after unsuccessful PTA of a severe stenotic renal artery of a functional kidney resulted in dramatic improvement in its function and the control of blood pressure [19].

Expert opinion & outlook

HHS is a rare and serious complication of arterial hypertension. It is prevalent in the youngest boys with congenital renovascular defects and in elderly females with acquired, severe atherosclerotic disorder. In both pediatric and adult patients, the physiologic background is more or less the same. If recognized in time and appropriately treated, HHS has a chance of being cured. Increasing awareness of HHS should result in an increasing rate of its diagnosis, appropriate investigations and treatment in hypertensive children. Prospective, multicenter registers are needed to determine the true prevalence of HHS in the pediatric hypertensive population.

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