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Differential diagnosis between the syndrome of inappropriate ADH secretion and cerebral salt-wasting syndrome[1)]

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Abstract

Hyponatraemia is one of the most common complications in patients with disorders of the central nervous system or those who have undergone cerebral neurosurgery. The differentiation between the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and the cerebral salt-wasting syndrome (CSWS) is important because the two diseases have different prognoses and require different specific treatment. Although most physicians are familiar with SIADH, they are much less familiar with CSW. This paper emphasizes the need for CSW to be included in the differential diagnosis of hyponatraemia; it reviews the aetiology, pathophysiology, treatment and differential diagnoses of CSW; particular attention is given to diagnostic laboratory markers, both those that are already established and those that are still under investigation.

Keywords: brain injury; hyponatraemia; subarachnoid haemorrhage.

Introduction

Hyponatraemia is one of the most frequent complications to follow brain trauma, subarachnoidal haemorrhage (SAB) or cerebral neurosurgery. In terms of causality, the hyponatraemia can be traced back to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or to cerebral salt-wasting syndrome (CSWS). The two syndromes have virtually identical clinical profiles, so the differential diagnosis can be very difficult, particularly in the early stages.

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Careful differentiation of the two syndromes is, however, of fundamental importance for therapy. Whereas SIADH is treated with restriction of fluids and/or the administration of diuretics, CSWS patients require sodium and volume replacement, when necessary in combination with mineralocorticoids. Hence, it is imperative to reach the correct diagnosis, since an inappropriate course of therapy can have dire consequences for the prognosis of the patient. In a study of 134 patients, 44 had hyponatraemia and 25 presented with the clinical picture of SIADH [1]. Of these 44 patients, 26 were subsequently treated by fluid restriction. However, under this SIADH-therapy, 21 patients (81%) suffered a cerebral infarct as an indirect indication of a possibly pre-existing CSWS that had been neither identified nor correctly treated. Laboratory analyses that would reliably differentiate SIADH from CSWS would therefore be extremely useful.

The present paper discusses the literature available regarding the already established and potential parameters for the differential diagnosis of SIADH and CSWS against the background of pathophysiology and clinical practice.

Epidemiology

Hyponatraemia is observed in 4–8% of patients up to ten days after excision of a cerebral tumour. In up to 2%, a symptomatic hyponatraemia occurs [2]. A study has reported appreciable hyponatraemia in as many as 9–35% of patients following surgery of the hypophysis; it was sometimes caused by SIADH, but more frequently by CSWS [3]. In a further study, hyponatraemia was found in 13.7% of 102 patients with medium-severe to severe symptomatic hyponatremia (SHT). SIADH was diagnosed in 12.9%, and CSWS in 1% [4]. This pattern was confirmed in a study of 316 patients with SAB, of whom 62 (19.6%) had significant hyponatraemia ($<$130 mmol/L). This was caused more often by SIADH (12.3%) than by CSWS (1.3%) [5].

Syndrome of inappropriate secretion of ADH (SIADH)

The syndrome of inappropriate secretion of ADH (SIADH) was first described by Schwartz and Bartter in 1957 [6]. It signifies an inadequate or pathologically high ADH secretion from the posterior lobe of the hypophysis. This

leads to a massive back-resorption of water from the renal collecting tubes and to the excretion of highly concentrated urine. Consequently, hyponatraemia arises through a volume surplus in the sense of dilution hyponatraemia. This pathogenic mechanism is exacerbated by the suppression of the renin–angiotensin–aldosterone system, and hence leads to natriuresis and secondarily to an increased excretion of water. Typically, in SIADH the regulation of the water budget is disturbed. However, there is no abnormality in the sodium excretion [7]. The volume budget is characterized by hypervolaemia, but often initially by euvolaemia [8].

The causes include cerebral lesions such as CNS tumours, SHT, SAB or neurosurgical procedures [4, 5, 9, 10], meningitis or encephalitis [10], severe infections such as pneumonia or HIV [11, 12], and medication such as serotonin reuptake inhibitors (SSRIs), or neuroleptic or chemotherapeutic agents [13, 14]. Further, the clinical appearance of SIADH can also arise as a result of a paraneoplastic release of ADH through tumours such as small-cell bronchial carcinoma [15], stomach carcinoma [16] or pancreatic tumours [17].

The increased secretion of ADH from the hypothalamus probably arises through stimulation or disinhibition of magnocellular neurones through various neural stimuli or neurotransmitters. Impaired inhibition of the magnocellular neurones by baroreceptors and volume receptors plays a role in this. These receptors are in the thorax, near the aorta, the large vessels and in the arteries of the heart, and their signals are relayed by the ninth and tenth cranial nerve via the brainstem to the hypothalamus. Every disturbance of these diffusely distributed volume receptors and baroreceptors in the thorax or CNS causes a reduction in the ADH-inhibition and thereby leads to increased secretion of ADH [18].

A volume excess is expressed clinically by hypertension and weight gain [7]. There is usually no oedema [7, 19]. The symptoms of acute hyponatraemia are caused essentially by brain oedema; symptoms include headaches, nausea, vomiting, muscle cramps, dizziness and lethargy [20]. Useful pointers for a slightly elevated blood volume that can be used in laboratory diagnostic procedures are a low normal reading for haematocrit, creatinine and urea. The sodium excretion in the urine is usually elevated ($>$20 mmol/L) despite hyponatraemia, and the osmolality of the urine is greater than the serum osmolality [18].

In addition to this clinical and laboratory-diagnostic evaluation, there is the possibility of measuring the ADH concentration. Abnormally high ADH concentrations have been found in patients with SIADH and a multiplicity of intracranial disturbances [21]. However, raised ADH concentrations must always be interpreted cautiously, since the secretion can also be stimulated by stress, pain, hypotension, or elevated intracranial pressure [22].

The therapy of choice is restriction of fluids. The fluid intake should be lower than the fluid loss and should be restricted to about 500–1000 mL/d. In severe acute hyponatraemia, sodium can be carefully introduced as a hyperosmolar solution [19]. In addition, careful administration of diuretics with furosemide may be indicated [3].

Cerebral salt-wasting syndrome (CSWS)

Cerebral salt wasting syndrome (CSWS) is defined through a renal loss of sodium in the context of cerebral injury, which leads to hyponatraemia and secondarily to a reduction in the extracellular volume [19]. The symptoms typically develop within the first ten days after a neurosurgical intervention [23], SHT [24] or stroke [25], or in the presence of a brain tumour [7].

The term CSWS was coined by Peters et al. in 1950 [26]. They described three patients with neurological disorders (encephalitis, SAB and bulbous poliomyelitis), who were characterized by hyponatraemia in combination with hypovolaemia in the presence of renal sodium loss [26]. The adrenocorticotropic axis was intact. Hence, it was concluded that the CSWS had been caused by a defect in the neural regulation of renal tubulus activity [27]. A subsequent study concerned 12 patients with intracranial problems (SAB, SHT and effects of neurosurgery), for whom the laboratory diagnosis fulfilled the criteria for SIADH. However, the blood volume was significantly reduced in ten of these twelve patients. These characteristics tallied with the concept of a CSWS [28].

The pathogenic mechanism of CSWS has not yet been clarified. Various theories, not necessarily mutually exclusive, are here discussed:

Disturbance of the neuronal influence on the kidneys and/or the central regulation of natriuretic factors probably play a decisive role. This leads to reduced sodium absorption in the proximal tubulus and secondarily to an osmotically determined loss of volume. The drop in the extracellular volume causes a stimulation of the baroreceptors in the hypothalamus and thereby a release of ADH from the posterior lobe of the hypophysis. In contrast to SIADH, the ADH secretion is in this case a physiological process that further exacerbates the hyponatraemia [7].

The sympathetic nervous system is involved in the control of the release of renin via β_1-receptors on the macula. Therefore, a reduced sympathicotonia in CSWS could explain the lowered concentrations of renin and aldosterone despite reduced extracellular volumes; these reductions lead also to reduced reabsorption of sodium in the kidneys and thereby to further fluid loss [29, 30]. Because of the low aldosterone, potassium excretion is also restricted, and so hypokalaemia is not one of the symptoms of CSWS [7].

Together with the disturbance in the neuronal influence on the kidneys, an inappropriate release of natriuretic factors can also be involved in the emergence of CSWS. In particular, ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide) are associated with the natriuresis in CSWS [29, 31]. Each of these proteins has a direct inhibitory effect on the release of renin from the

juxtaglomerular cells and on the release of aldosterone from the adrenal gland, which then leads to renal loss of sodium and fluids (see Figure 1 [7]).

The clinical characteristics of CSWS therefore result from hyponatraemia and hypovolaemia. The main features are orthostatic dysregulation, tachycardia, weight loss, nausea, vomiting and signs of exsiccosis such as dry mucosae, persistent skin folding and haloed eyes, apathy and dizziness. Laboratory tests reveal signs of a haemoconcentration with elevated haematocrit and serum protein as well as, in certain cases, elevated concentrations of urine-binding substances (creatinine, urea). In patients with invasive haemodynamic monitoring there is a low pulmonary-arterial pressure ($<$8 mm Hg) or central-venous pressure ($<$6 mm Hg).

The basis of therapy for CSWS is replacement of fluid and sodium. Intravenous hydration with physiological salt solution (0.9% NaCl) [32] can be used alone or in combination with hypertonic solution (3% NaCl) [20] or oral administration of common salt [7, 32]. This should be regulated in accordance with the severity and symptoms of the disorder. The sodium balance should not exceed 8–10 mmol/L within 24 h, in order to minimize the risk of pontine myelinolysis [8, 33]. In order to reduce renal salt loss, the mineral corticoid fludrocortisone can be added [3, 34]. It reacts directly on the renal tubulus and leads to increased reabsorption of sodium. In one study, a dose of 2$\times$0.2 mg i.v. or p.o. significantly improved the salt and volume balance [35]. CSWS is a transient disorder that retreats after an average of three to four weeks [7].

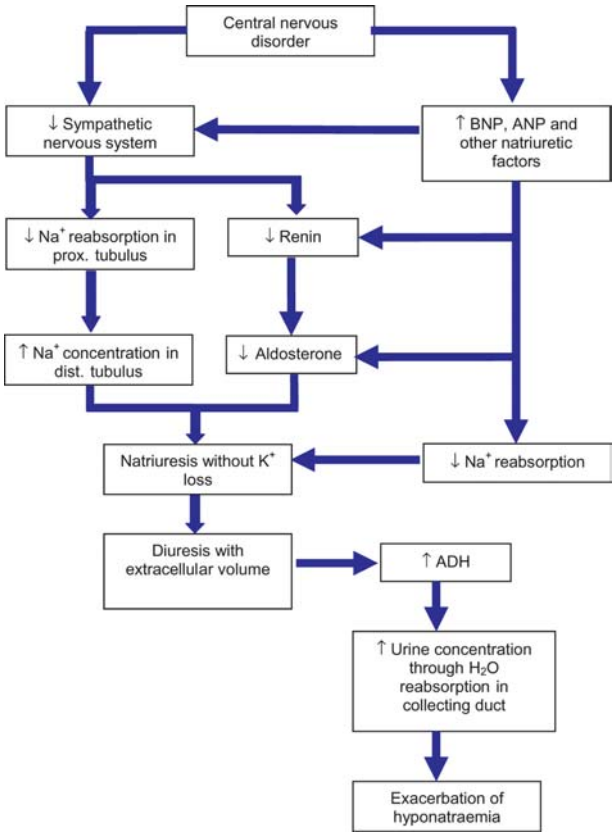

Figure 1 Pathophysiological mechanisms in the development of hyponatraemia in CSWS (modified after [7]).

Natriuretic peptides in connection with CSWS

Studies have identified further potential factors that may cause natriuresis and could be used to differentiate between SIADH and CSWS. Promising parameters include ANP (atrial natriuretic peptide), BNP (brain natriuretic peptide), OLC (ouabain-like compound) and oxytocin.

ANP

In rats, injection of atrial myocardial extract led to a 10-fold increase in diuresis and a more than 30-fold increase in natriuresis [36]. This effect was mediated through the peptide hormone ANP, which is produced, stored and secreted predominantly in the right atrium [37]. In addition, ANP-containing neurones have been identified in the hypothalamus [38]. However, the concentration of the cerebral ANP is several decimal powers lower than in heart muscle [39], so that a cerebral release of ANP probably can not be held responsible for the development of CSWS. The physiological stimulus for the ANP release is the distension of the atrium with expansion in volume [37]. In the epithelial cells of the tubulus, ANP inhibits reabsorption of sodium and leads thereby to increased natriuresis and diuresis. Furthermore, it has a direct inhibitory effect on the release of aldosterone in the adrenal glands and on the release of renin in the macula [40].

There are indications that the central nervous system modulates the cardiac ANP secretion. In one study, six out of eight patients with various neurological disorders had a distinctly elevated ANP, which was correlated virtually linearly with the sodium excretion in the urine [21]. Further, raised levels of ADH and ANP were reported in a patient with SAB up to the fifth day after the event; while the ADH slowly returned to normal, the ANP remained distinctly high and was associated with prolonged hyponatraemia [41]. A study of 20 patients with SAB gave similar results [42]: 11 of these 20 patients were hyponatraemic and had elevated concentrations of ADH and ANP up to the second day after trauma; the ANP remained high until Day 14, whereas the ADH concentration fell significantly during the second week [42]. These results could indicate that SIADH develops immediately after the haemorrhage; however, a prolonged hyponatraemia accompanies a persistent elevation of plasma ANP [19].

Nevertheless, it has not been possible to confirm the relationship between ANP and CWS in all studies. Of 25 patients with intracranial aneurysms, only those 21 with SAB caused by a rupturing aneurysm had elevated concentrations of ANP [43]; interestingly, there was no cor-

relation between the ANP concentration and the sodium in the serum. Two of the 21 patients had appreciable hyponatraemia, but their ANP concentrations did not differ from those of patients without this electrolyte imbalance. Further, normal ANP concentrations were found in patients with CSWS with gliomas [44] and a variety of intracerebral haemorrhages [21], as also after surgery on the hypophysis [23]. Taken together, the data show that ANP participates in the development of CSWS but is not solely responsible for it.

BNP

BNP is a cyclic polypeptide and was first identified in pig brain [45]. However, most of it (60–80%) occurs in the ventricle, some produced and secreted in the atrium of the heart [31]. The physiological stimulus that triggers the secretion is the increase in pressure and the distension of the ventricle [37]. As well as having a structure very similar to that of ANP, it also has similar effects [45].

It has been shown that BNP is a potential factor for the development of CSWS [29]. Elevated concentrations have been found in all patients with SAB. The concentration of peptides is significantly correlated both with sodium excretion and volume excretion and also with the intracranial pressure reading. Further, a three- to six-fold rise in concentration of ANP and BNP has been reported in nine patients on the first to fifth day after neurosurgery [46]. Sodium excretion in urine was elevated in all patients. In another study, elevated concentrations of BNP were recorded in the plasma of patients with SAB and hyponatraemia [42].

However, the data regarding BNP are not homogeneous. So in a study of 24 rats with CSWS against a background of induced SAB there was a significant increase in ANP. The BNP concentration, on the other hand, remained unchanged [47]. Another example comes from an investigation of rats after SAB, in which significant natriuresis and diuresis with negative sodium balance were unrelated to the BNP secretion [48].

OLC

OLC is a mineralocorticoid produced predominantly in the adrenal cortex (zona fasciculata), hypothalamus and cardiac muscle. Physiologically, it is released during many physical activities and by stress, and can therefore be counted among the stress hormones [49]. In addition, it plays a role through the modulation of Na^+-K^+-ATPase of the renal tubulus cells in the regulation of natriuresis and diuresis [50, 51].

OLC, too, has been studied in connection with the pathogenesis of CSWS. In experiments with rats, autologous infusion of venous blood into the cerebral ventricle initiated SAB. This led to an increase in serum OLC in combination with natriuresis and an increase in volume of urine. In the course of this, the sodium excretion was correlated with ouabain activity [52]. These data indicate that, in the context of SAB, the OLC activity has a basic influence on natriuresis and the regulation of urine volume. It has been shown that in rats the intracerebroventricular infusion of a hypertonic solution stimulated natriuresis [53]. This could be blocked through the intraventricular injection of a specific digoxin antibody, which inhibits the OLC function, whereas an intravenous application of the antibody had no effect [53]. The observations suggest that OLC is implicated in the development of CSWS through central modulation. This supposition has been supported by the results of a study in which ouabain was administered into the cerebroventricle of rabbits with one intact and one denervated kidney. This injection caused a prompt natriuresis and diuresis in the denervated kidney [54]. It has also been suggested that, with CSWS too, an impaired neuronal influence on the kidneys may be a possible pathogenetic mechanism [7]. However, further research is required before the precise mode of action of OLC in this connection can be clarified.

Oxytocin

Oxytocin is a hormone produced in the magnocellular neurones of the hypothalamus, and stored and secreted in the posterior lobe of the hypophysis. It is distributed in response to a wide variety of stimuli, including stress. This is another substance whose role in natriuresis has been experimentally demonstrated [55, 56]. There are few data in the literature concerning the secretion of oxytocin after SHT, SAB or cerebral neurosurgery. So far, there has been only one report of an elevated concentration of oxytocin in the plasma after SAB [57]. The role of this hormone in the development of CSWS requires further investigation.

Laboratory differential diagnosis of SIADH and CWS

In order to achieve a diagnosis of either SIADH or CSWS, other possible causes of hyponatraemia must first be ruled out. These include endocrine disorders such as hypothyroidism or adrenal cortex insufficiency. These are easily possible through measurement of TSH and the free thyroid hormone, or by a low-dose ACTH test. Hyponatraemia can often also be attributed to hyperglycaemia; for example, an increase of 5.6 mmol/L (100 mg/dL) in blood sugar is accompanied by a decrease of ~1.7 mmol/L in serum sodium [58]. Possible causes for this may include kidney failure with disturbance of the water excretion and/or sodium loss, or an exsiccosis with loss of electrolytes through diarrhoea or uncontrolled diuretic therapy. Further, other causes might be a decompensated cardiac insufficiency or liver cirrhosis; these pose no significant diagnostic problems, but as part of an exclusion diagnosis would be an important contribution towards effective therapy.

Table 1 Differential diagnosis and therapy of cerebral salt-wasting syndrome (CSWS) in comparison with the syndrome of inappropriate ADH-secretion.

	CSWS	SIADH
Na-Serum	↓	↓
Na-Urine	↑↑	↑
Urine quantity	↑	↓
Osmol-Urine	↑-n	↑↑
Osmol-Serum	↓-n	↓
CVP/RR	↓	↑
Plasma volume	Hypovolaemia	Eu/Hypervolaemia
Uric acid	↓-n (Persistence after balance of Na and volume)	↓ (Normalization after balance)
Creatinine/Urea	↑	↓
Haematocrit	↑	↓
ADH	↑-n	↑↑
ANF	n	↑
BNP	↑	↑
OLC	↑ (?)	(?)
Oxytocin	↑ (?)	(?)
Therapy	• Volume • NaCl i.v. or p.o. • Hydrocortisone • Fludrocortisone (initial 2×0.2 mg)	• Restriction of fluids (0.5–1 L/d) • Diuretics where applicable (Furosemide) • With severe symptoms Hyponatriaemia slow infusion of 3% NaCl sol.

The clinical distinction between SIADH and CSWS can be difficult right from the outset, since each syndrome is characterized by hyponatraemia and high sodium excretion and osmolality in the urine. The typical criteria are summarized in Table 1. Special care must, therefore, be given to the determination of the volume status, the chief clinical differential criterion.

Further, the determination of BNP is a reliable indicator in the diagnosis of CSWS. Since the determination of BNP has already found a place in laboratory diagnosis, this method can be regarded as established. On the other hand, measurements of ANP or ADH can not differentiate between SIADH and CSWS. Studies of the natriuretic peptides OLC (ouabain-like compound) and oxytocin are encouraging but have so far been confined to clinical research and can not yet be recommended for routine use.

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