Review

Biochemical factors involved in the pathophysiology of cerebral salt wasting syndrome following subarachnoid haemorrhage.

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Abstract

Introduction: Cerebral salt wasting syndrome (CSWS) and syndrome of inappropriate anti diuretic hormone (SIADH) secretion are the most common aetiological factors for developing hyponatremia following stroke. Though extracellular volume status is the key feature that helps to differentiate these two syndromes assessing the volume status is not an easy task. However, the differentiation of these two entities is crucial as the treatment options are completely different. Hence knowledge of the pathophysiological factors of CSWS is important to make an accurate diagnosis of CSWS. The objective of this review is to systematically evaluate the articles about the biochemical factors which involve in the pathophysiology of CSWS following subarachnoid haemorrhage (SAH).

Methods: A review of literature published in English was conducted in PubMed database without a date limitation. Three sets of search terms were used. The first set consisted of Medical Subject Heading (MeSH) terms"Cerebral salt wasting" and "Stroke". The second set included the MeSH terms "Hyponatremia" and "Subarachnoid haemorrhage". The last set included "Cerebral salt wasting" and "Subarachnoid haemorrhage". Articles containing at least one word from each set were reviewed.

Results: At least one MeSH term from each set was incorporated in 296 articles. Of these, 163 were rejected as they were not related to cerebral salt wasting and subarachnoid haemorrhage.The association between the pathophysiology of natriuretic peptides and CSWS have been studied many times. There was only one study which evaluated the effect of cerebrospinal fluid adrenomedullin (CSF AM) on pathophysiology of CSWS.

Conclusion: Natriuretic peptides are involved in the pathophysiology of CSWS. However, the exact peptide which can cause CSWS is not well proven.

Keywords: Cerebral Salt Wasting Syndrome, Cerebrospinal fluid adrenomedullin, Natriuretic peptides, Subarachnoid haemorrhage, Syndrome of Inappropriate Anti Diuretic Hormone secretion

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Introduction

Stroke is a leading cause of mortality which results in 5.7 million deaths per year worldwide [1]. Moreover, it results in a huge disease burden calculated by Disease Adjusted Life Years (DALYs) [2]. It was reported that approximately 113 million DALYs had been lost due to stroke [3]. According to data published by the world health organization in 2001, a higher percentage (87%) of deaths from stroke occur in low and middle-income countries of which 40% occur in South Asian countries [4].

Hyponatremia is a common electrolyte disorder seen in neurosurgical patients. It can cause increased morbidity and mortality [5]. Hyponatremia has been cited as an independent predictor of stroke mortality [6]. In stroke, hyponatremia is frequently hypoosmolar and it can be due to either Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) or Cerebral Salt Wasting Syndrome (CSWS) [7].

Many studies have shown increased incidences of hyponatremia following subarachnoid haemorrhage (SAH) compared to other types of stroke. Sherlock et al have shown the incidence of hyponatremia following SAH is as high as 56.6%) [8]. Several studies have shown that CSWS is the most common aetiological factor for developing hyponatremia following SAH. However, there was one study in which the researches have not found even a single case of CSWS [9]. Most of the literature suggest that CSWS and SIADH both contribute to the development of hyponatremia.

Both SIADH and CSWS share many clinical and laboratory features in common [10]. However, the extracellular fluid volume status is the crucial factor in differentiating these two syndromes. Extracellular fluid volume is slightly higher in SIADH compared to CSWS [10]. However, assessing the volume status is not an easy task [10]. Still the differentiation of these two syndromes is extremely important as the therapeutic approach is totally different in each disorder. Replacement of sodium and fluid is the mainstay of treatment in CSWS [11]. In contrast, fluid restriction is recommended in SIADH [11].

Since the differentiation of these two syndromes is of paramount importance, it is useful to know the pathophysiology of CSWS. Therefore a literature review was conducted to find out about the availability of such evidence.

Objective: To systematically review articles that are published about biochemical factors involved in the pathophysiology of CSWS following SAH.

Methodology

A systematic review on literature published in English was conducted in PubMed database without a date limitation. Both human and animal studies were included. Three sets of search terms were used. The first set consisted of Medical Subject Heading (MeSH) terms “Cerebral salt wasting” and “Stroke”. The second set included the MeSH terms “Hyponatremia” and “Subarachnoid haemorrhage”. The last set included “Cerebral salt wasting” and “Subarachnoid haemorrhage”.

Results of the database search:

At least one MeSH term from each set was incorporated in 296 articles. Of these, 163 were rejected as they were not related to CSWS and SAH. Articles containing at least one word from each set were reviewed.

Of the 134 articles, 9 articles related to biochemical parameters (natriuretic peptides and cerebrospinal fluid adrenomedullin-CSF AM) which involve in the pathophysiology of CSWS following SAH were identified (Fig 1).

Results

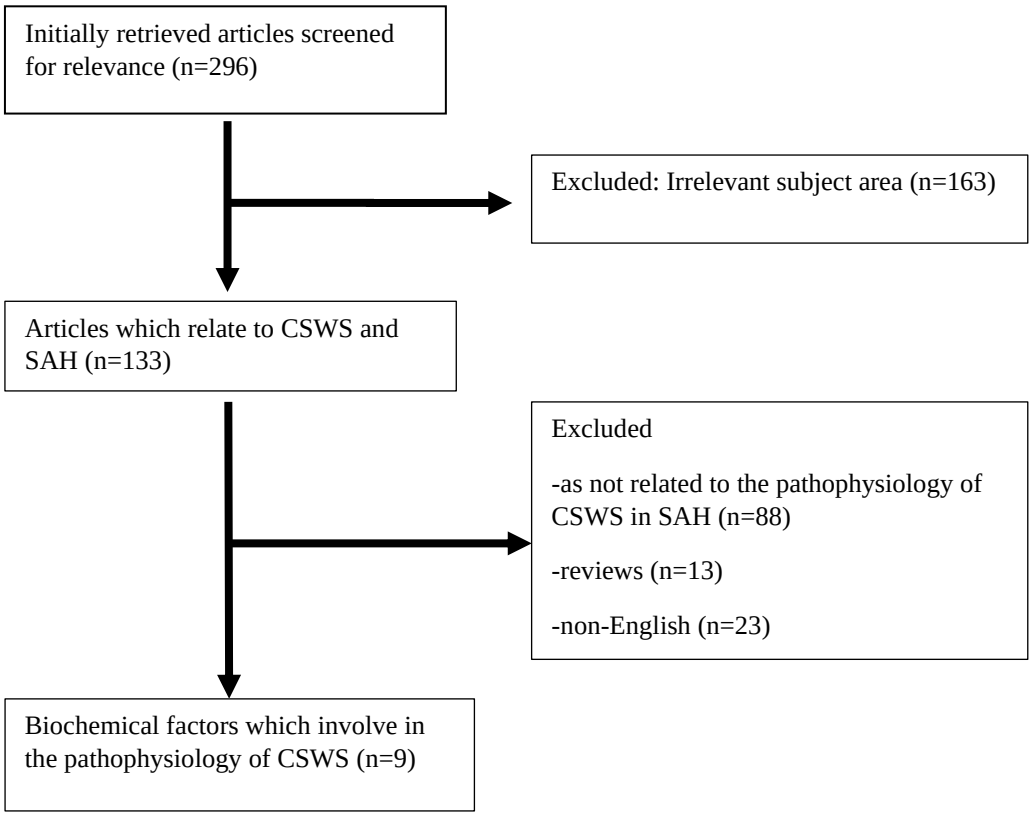
There were 09 articles on the biochemical factors which involve in the pathophysiology of CSWS after SAH. All of them were prospective studies. Eight of those studies investigated the relationship between the CSWS and the natriuretic peptides after SAH. One study investigated about the relationship of CSF AM and CSWS after SAH.

Biochemical factors involve in the pathophysiology of CSWS

Literature on biochemical parameters related to the pathophysiology of CSWS in SAH include measurement of atrial natriuretic peptide (ANP),brain natriuretic peptide(BNP),C-type natriuretic peptide (CNP)and CSF AM.

A study done in 2009 by Audibert et al using 19 patients revealed that despite relatively well preserved electrolytes and water, the reduction in circulating blood volume cannot be prevented in severe SAH patients [12].

Fig 1: Selection process of studies



This finding is in favor of salt wasting and they have excluded the hypothesis of SIADH. Both ANP and BNP levels increased with no correlation between the concentrations of two natriuretic peptides and natriuresis. One major concern of this study is that all SAH patients are treated with standardized Na^+, water and norepinephrine to prevent the onset of hyponatremia which can influence the release of natriuretic peptides.

Berendes et al have compared the ANP, BNP, CNP, anti diuretic hormone (ADH), renin, aldosterone and cortisol levels in 10 patients with SAH, 10 cerebral tumor resected patients and normal healthy control group. It was found that the Higher BNP concentration in SAH group compared to the control group was identified. In contrast, the tumor group showed values similar to control group. Further, linear regression analysis showed a significant correlation between BNP concentration and urinary Na^+excretion.. Therefore it was concluded that increased BNP levels can induce salt wasting [13]. Although the extracellular volume status was suggested as the main distinguishing factor between SIADH and CSWS, a volume assessment was not conducted when differentiating CSWS and SIADH.

Using 20 patients, Isotani et al in 1994 have studied about the relationship among natriuretic peptides, ADH plasma concentrations and hyponatremia after SAH . A significant change in BNP concentration between patients with SAH and the control group was not revealed. Authors have concluded that CSWS as the reason for the hyponatremia in SAH. Further they have suggested that ANP is the causative factor for the observed pathophysiological change. A correlation between plasma ANP concentration and hyponatremia was identified by the second week following SAH [14]. However, the researchers have not performed a proper evaluation of the hyponatremia in this study by doing serum osmolality and urine osmolality levels.

In 2004, using an animal modelKojima et al investigated the relationship between CSWS and natriuretic peptides in rats with SAH [15]. .Using body weight and hematocrit the researchers have assessed the volume status of the rats who developed CSWS due to SAH. However, use of only two parameters is not recommended to obtain the volume status in SAH. Both clinical and biochemical data should be considered cumulatively to arrive at an accurate diagnosis of hypovolemia [16]. This study did not identify a significant difference of BNP and ADH concentration

betweenrats with SAH and sham rats. Interestingly, researchers have found a significant decrease ($p<0.05$) of ANP concentration in SAH rats to that of sham rats. Therefore authors have concluded that neither ANP, BNP nor ADH responsible for initiating CSWS [15].

A study done by Wijdicks et al in 1991 using 14 SAH patients treated in intensive care unit (ICU) has revealed that there are two peaks of atrial natriuretic factor (ANF) expression after SAH. The delayed peak is related with increased natriuresis and negative Na^+ balance. With these results, the study concluded that the natriuresis in SAH is due to CSWS. Further, ANF was proposed as a possible causative factor as it significantly increased before the onset of natriuresis [17]. However, the researchers have not done an assessment of the plasma volume of the patients. Moreover, the fluid therapy and electrolytes were well controlled in these patients as they were treated in ICU and that can influence the natriuretic peptide release.

Dorhout Mees et al conducted a case-control study to detect the possibility of using BNP to differentiate hypovolemic hyponatremia and non-hypovolemic hyponatremia. As both groups of this case-control study (n=58 patients showed increased BNP concentrations, it was concluded that BNP cannot be used to differentiate hypovolemic hyponatremia and non –hypovolemic hyponatremia [18].

In three studies SIADH was not considered as an entity of hyponatremia [19-21]. Instead in these studies, all the cases of hyponatremia were attributed to cerebral salt wasting. Kubo et al in 2008 investigated the correlation between ANP, BNP, plasma and CSF adrenomedullin (AM) and the development of hyponatremia in 32 patients with SAH. Eventhough a significant rise of ANP level was not detected BNP level was found to be elevated at the late period of SAH. However, according to the results of the multivariate analysis only CSF AM in late period of SAH showed a significant association with hyponatremia [19]. Increased secretion of CSF AM in patients with SAH is probably due to the cerebral hypoperfusion caused by post-SAH vasospasms.

In another similar study possibility of using elevation in serum BNP levels as a predictive marker in developing delayed ischaemic neurological deficits (DIND) in SAH patients was investigated [20]. Results of 40 patients revealed a significant correlation between BNP and DIND and hence elevated BNP was proposed as an effective marker in diagnosing DIND and impending CSWS in patients with SAHandlow Glasgow Coma Scale (GCS) score [20]. This finding is important in guiding the therapeutic management as the low GCS score patients are difficult to assess clinically. However, their conclusion is controversial as all hyponatremic patients may not belong to the group of CSWS.

Another study done by Nakagawa et al in 2010 have again considered the cause of hyponatremia following SAH was purely CSWS. Using 39 patients whether the increased level of ANP precede the onset of hyponatremia was investigated to assess the possibility of using it as a marker in predicting the DIND. A significant rise in serum ANP levels but not in the serum BNP levels was detected in hyponatremia group compared to normonatremic group. However, the researchers failed to find a correlation between ANP and hyponatremia. Therefore it was concluded that there is another factor which is responsible for CSWS, and ANP is contributed only for the initiation of hyponatremia [21]. Throughout the study as all the patients were kept normovolemic and normotensive, there is a possibility that the fluid therapy can influence the release of natriuretic peptide.

Conclusion

Natriuretic peptide theory is a frequently discussed pathophysiological mechanism for CSWS. ANP, BNP, C-type natriuretic peptide and dendroaspis natriuretic peptide are the natriuretic peptides which involve in the pathophysiology of CSWS [22]. It is believed that out of all natriuretic peptides, BNP may act as the main determinant of CSWS [22]. In contrast it is suggested that apart from ANP and BNP, there could be another natriuretic factor which cause CSWS [23]. The natriuretic effects of these peptides are mediated by inhibiting the Renin-Angiotensin- Aldosterone system, promoting afferent arteriolar dilatation and increasing the glomerular filtration [24]. The usual sites of secretion of ANP and BNP are cardiac atria and ventricles respectively [25]. However, the mechanism of releasing these peptides in intracranial disorders is not well established [25]. According to the results of our review, we can conclude that natriuretic peptides have a role in the pathophysiology of CSWS. However, the exact peptide which is involved in the occurrence of CSWS is not well proven.

Adrenomedullin (AM) is also considered as a factor in the pathophysiology of CSWS [11]. It is found in both plasma and cerebrospinal fluid. The natriuretic and diuretic activity is mediated by its potent vasodilator properties and ability of decreasing the renal sympathetic

activity [11]. The results of the review favors the fact that CSF AM is involved in the pathophysiology of CSWS. However further studies are needed to evaluate the association between CSWS and CSF AM as the literature on this area is scarce.

We would like to recommend the following facts when planning future studies on evaluating the pathophysiological factors of CSWS following stroke. Firstly the initial differential diagnosis should include both SAIDH and CSWS. Secondly, the volume assessment of the patients should be done properly as it is the key to differentiate CSWS and SIADH. This will help to arrive at the accurate diagnosis of CSW

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