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# Hyponatremia and aneurysmal subarachnoid hemorrhage, does salt loss exist?

Pierre-Antoine Pioche

► **To cite this version:**

Pierre-Antoine Pioche. Hyponatremia and aneurysmal subarachnoid hemorrhage, does salt loss exist?. Human health and pathology. 2020. dumas-03263432

**HAL Id: dumas-03263432**

**<https://dumas.ccsd.cnrs.fr/dumas-03263432>**

Submitted on 17 Jun 2021

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UNIVERSITÉ CLERMONT AUVERGNE

UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

PIOCHE Pierre-Antoine, Thibaut

Présentée et soutenue publiquement le 03 septembre 2020

HYPONATREMIE ET HEMORRAGIE SOUS-ARACHNOIDIENNE ANEVRYSMALE,  
EXISTE-T-IL UNE PERTE EN SEL ?

HYPONATREMIA AND ANEURYSMAL SUBARACHNOID HEMORRHAGE,  
DOES SALT LOSS EXIST ?

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**Président du jury :** Monsieur BAZIN Jean-Etienne, Professeur, UFR de Médecine et des professions paramédicales de Clermont-Ferrand, Anesthésiologie et Réanimation chirurgicale.

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## REMERCIEMENTS

**Monsieur le Professeur Jean-Etienne BAZIN**, votre bienveillance et vos conseils m'ont accompagné depuis les blocs opératoires du désert marocain jusqu'à ceux de Clermont-Ferrand. Je vous remercie de nous offrir, à nous, internes d'anesthésie-réanimation, un environnement de formation serein dans lequel nous avons pu nous épanouir malgré les exigences de la spécialité. Je vous remercie d'accepter aujourd'hui de présider ce jury.

**Monsieur le Professeur Emmanuel FUTIER**, je mesure la chance d'avoir bénéficié de votre enseignement tout au long de mon internat. Votre qualité de chercheur, votre proximité des étudiants sont des atouts majeurs pour notre spécialité. Votre bienveillance est des plus exceptionnelles, votre qualité de toujours valoriser le travail réalisé l'est également. Vous compter parmi le jury de mon travail de thèse est un honneur. Soyez assuré de mon plus grand respect.

**Monsieur le Professeur Alexandre LAUTRETTE**, mon premier mentor. Merci pour tout, sincèrement. Merci de m'avoir accompagné vers la réanimation médicale et de m'avoir encadré comme personne ne l'avait fait avant. Merci ensuite de m'avoir soutenu dans des projets différents, qui me mènent aujourd'hui vers l'anesthésie-réanimation. Travailler à vos côtés était un honneur, et encore plus, un vrai plaisir. Je vous remercie aujourd'hui d'accepter de juger mon travail de thèse.

**Monsieur le Docteur Damien Bouvier**, je te remercie d'avoir accepté aujourd'hui de juger ce travail. Si nos parcours ne se sont que peu croisés, je sais tes qualités d'enseignement et de recherche ; je connais ta rigueur et ta détermination que je prends pour modèle.

**Monsieur le Docteur Russell Chabanne**, ces quelques lignes ne suffiront malheureusement pas. Tu es tout simplement le médecin, le mari et le père de famille que je rêve de devenir. Travailler à tes côtés m'a redonné goût à la vraie médecine, au patient avant tout. Ta faculté à mener de front tous tes combats est une source de motivation inépuisable pour tes équipes. On mesure souvent les qualités d'un médecin aux facilités qu'on aurait à lui confier nos proches et je le ferais sans le moindre doute.

**Marion**, mon amour. Tu es cette rencontre que l'on ne fait qu'une fois. Avancer à tes côtés est un pur bonheur, que je savoure à chaque instant. Tu es la chance de ma vie ; que la nôtre soit merveilleuse. Je t'aime à l'infini.

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## LIST OF ABBREVIATIONS

<b>aSAH</b>	Aneurysmal Subarachnoid Hemorrhage
<b>CERAR</b>	Committee of Research and Ethics of Anesthesia and Intensive Care
<b>CI</b>	Confidence Intervals
<b>CNIL</b>	National Commission on Informatics and Liberty
<b>CSW</b>	Cerebral Salt Wasting syndrome
<b>CT</b>	Computed Tomography
<b>DCI</b>	Delayed Cerebral Ischemia
<b>ddAVP</b>	Desmopressin
<b>eGFR</b>	Estimated Glomerular Filtration Rate
<b>GOS</b>	Glasgow Outcome Scale score
<b>hNa</b>	Hyponatremia / Hyponatremic (patients)
<b>ICD</b>	International Statistical Classification of Diseases and Related Health Problems
<b>ICU</b>	Intensive Care Unit
<b>IQR</b>	InterQuartile Range
<b>ISW</b>	Iatrogenic Salt Wasting
<b>LOS</b>	Length Of Stay
<b>M ± SD</b>	Mean ± Standard Deviation
<b>MAP</b>	Mean Arterial Pressure
<b>MRI</b>	Magnetic Resonance Imaging
<b>(n) p</b>	(number) patients
<b>no.</b>	Number
<b>OR</b>	Odds Ratio
<b>rFischer</b>	Fischer's revisited scale
<b>SAH</b>	Subarachnoid Hemorrhage
<b>SIADH</b>	Syndrome of inappropriate antidiuretic hormone
<b>TSH</b>	Thyroid Stimulating Hormone
<b>WFNS</b>	World Federation of Neurosurgical Societies

## INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is characterized by blood extravasation into the peri and intracerebral meningeal layers due to arterial aneurysmal rupture. (1) Hyponatremia (hNa) is defined as serum sodium concentration  $<135 \text{ mmol.L}^{-1}$  and occurs in up to 50% of patients with aSAH. (2) Hypotonic hNa contributes to increase intracellular volume and is associated with cerebral edema, intracranial hypertension, seizures and poor neurological outcome. (3) In aSAH, hNa is related to inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting syndrome (CSW). (4) In clinical practice, distinction between the two conditions is difficult but critical since treatments are different. (5-7) CSW is a disorder in sodium and water control in the setting of normal kidney function. It is characterized by urinary salt loss leading to hyponatremia and hypovolemia. Proposed mechanisms for natriuresis in CSW included increased atrial natriuretic peptide, decreased kidney sympathetic tone and suppressed aldosterone secretion despite volume depletion. (8) Nevertheless, evidence unequivocally implicating any of these mechanisms has not been demonstrated. (9) CSW diagnosis is based on hyponatremia, hypovolemia, hypo-osmolality, elevated urine osmolality ( $>100 \text{ mOsm.kg}^{-1}$ ) and elevated urinary sodium concentration ( $>40 \text{ mmol.L}^{-1}$ ). (8) According to these heterogeneous criteria, CSW incidence in SAH varies according to studies from 6.5% to 94% (10-13). To avoid discrepancy associated with the use of composite diagnostic criteria, measuring salt loss in hNa after aSAH could be an objective criterion of CSW. (5,6,10,14). Due to the presumed mechanism of salt loss in CSW, medication with mineralocorticoid activity, such as fludrocortisone acetate, may decrease natriuresis and are indicated for treatment of hNa in aSAH. (15,16) In the present study, we explored hNa and



salt loss in a monocentric retrospective cohort of aSAH patients and assessed CSW incidence, mineralocorticoids effect and outcomes.

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## **METHODS**

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### **DATA SOURCES**

Data were collected for patients hospitalized in the 13 beds Neurological Intensive Care Unit (ICU) of the Clermont-Ferrand University Hospital, France, which takes care of the majority of aSAH patients in a region of 1.4 millions inhabitants, between November 1<sup>st</sup>, 2012, and May 1<sup>st</sup>, 2020. In our hospital, aSAH are systematically admitted in ICU. Patients with diagnosis of SAH, hydrocephalus and intraventricular hemorrhage were identified using the ICD 10 and 11 electronic coding system (Codes I60, I615 and G91). We included consecutive patients with aSAH. Exclusion criteria were hNa on the day of hospitalization and a history of severe renal failure (estimated Glomerular Filtration rate < 30 mL.min<sup>-1</sup>), congestive heart failure and endocrine disorders (central diabetes insipidus, unstable hypothyroidism or hypopituitarism). As a local protocol, electrolytes and biochemical parameters were recorded daily in plasma and urine samples of patients with aSAH. hNa patients without urine data were excluded. Every patient was evaluated at 3 months in the neurosurgery clinic with brain imaging. Clinical, radiological and biochemical parameters were extracted from hospital and ICU electronic medical records of enrolled patients.

### **STUDY OVERSIGHT**

This study was approved by the French Ethical Committee for Research in Anesthesia and Intensive Care (Comité d’Ethique pour la Recherche en Anesthésie-Réanimation, CERAR, [www.sfar.org](http://www.sfar.org), IRB 00010254 – 2020 – 075). Anonymization and data privacy were ensured

according to French data protection regulation committee (Commission Nationale de l'Informatique et des Libertés, CNIL).

## **STUDY ENDPOINTS**

The primary endpoint was the measure of salt loss in hNa patients to assess incidence of CSW in aSAH. Secondary end points were the evaluation of 1 year mortality and neurological outcomes (including vasospasm, delayed cerebral ischemia (DCI) and Glasgow Outcome Scale (GOS) at 3<sup>rd</sup> month) in hNa patients with or without salt loss. Effect of mineralocorticoid treatment in hNa was also analysed.

## **aSAH MANAGEMENT AND STUDY DEFINITIONS**

### *SAH*

SAH was confirmed by imaging or lumbar puncture. Severity of SAH was classified based on initial CT scan according to Fischer's revisited scale (rFischer) and to World Federation of Neurosurgical Societies (WFNS) classification correlated to the clinical status of the patient at the time of presentation. (17,18)

### *Aneurysm description and position*

CT angiography or three-dimensional angiography was performed to diagnose an aneurysm and conclude to aSAH. (19) Aneurysm position was confirmed by cerebral angiography. If several aneurysms coexisted, the one considered to be responsible for SAH was documented.

### *Initial Treatment*

Aneurysm occlusion was achieved by means of endovascular coiling as the preferred technique or by surgical clipping within 24 hours after hospital admission. Standard treatment

of patients with aSAH included calcium channel blockers with Nimodipine for 21 days to prevent DCI.

### *Hyponatremia*

hNa was defined as a decrease in the serum sodium concentration to a level below  $135\text{mmol.L}^{-1}$  on at least one blood sample during the ICU stay. (20) hNa was only considered if serum tonicity was lower than  $280\text{mOsmol.L}^{-1}$  to avoid hypertonic hyponatremia.

### *Salt loss*

Sodium balance was measured by the difference between sodium intakes and urinary sodium loss from ICU admission to the day hNa diagnosis. Salt loss was confirmed by a negative sodium balance, that is to say if sodium loss exceeded sodium intakes. Sodium intakes were calculated from all perfusate containing sodium, all fluid therapies and all digestive intakes (enteral and oral nutrition). Sodium loss were calculated by cumulative urinary loss of sodium on a continuous daily evaluation.

### *CSW*

CSW was defined by salt loss leading to hyponatremia. (9,21,22) Salt loss due to drugs as ddAVP (desmopressin), milrinone or natriuretics were defined as iatrogenic salt wasting (ISW) and were excluded from the diagnosis of CSW.

### *Vasospasm and delayed cerebral ischemia*

Narrowing of angiographically visible arteries between 4 and 14 days after the onset of aSAH was defined as vasospasm. (23) Transcranial Doppler ultrasonography was used as a daily screening tool for the presence of cerebral vasospasm and when elevated mean flow velocities suggested spasm, diagnostic confirmation was standardly done with angiography. (24)

DCI was defined as a clinical syndrome of focal neurologic deficit and/or Glasgow Coma Scale decline  $\geq 2$  points compared to previous one, that appeared in patients after aneurysm occlusion due or not to a vasospasm and that could not be explained by other causes of neurological deterioration as rebleeding, hydrocephalus, electrolyte disturbance or seizures. (25) Additional ischemic radiological lesion on CT or MRI, absent on the initial evaluation and after aneurysm occlusion, at one month from aSAH was also considered as DCI. (26)

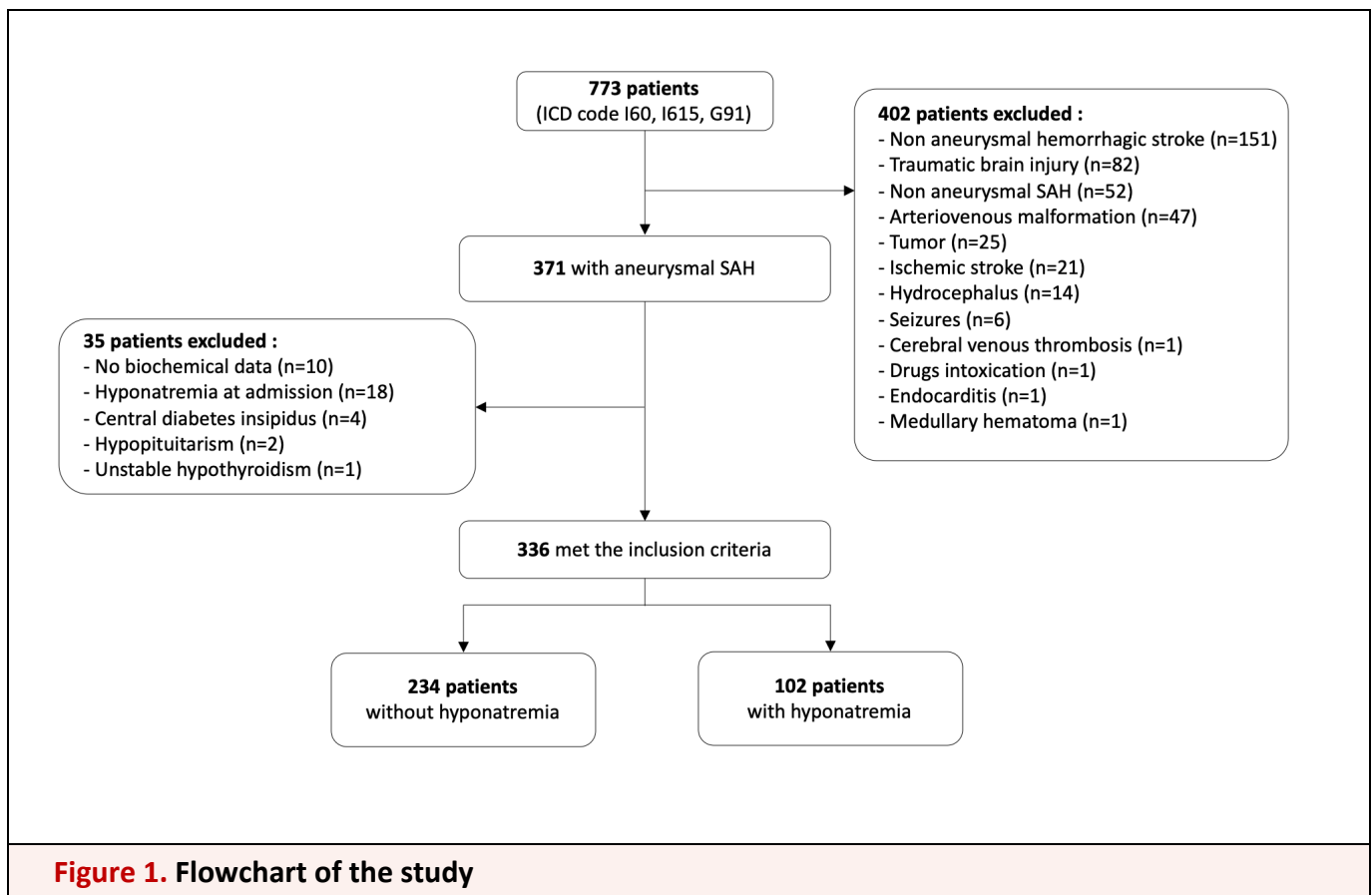
## **STATISTICAL ANALYSIS**

Statistical analysis was performed using Stata software (version 15 ; StataCorp, College Station, Texas, USA). All tests were two-sided, with a Type I error set at 0.05. Categorical parameters were expressed as frequencies and associated percentages, and continuous data as mean  $\pm$  standard deviation or as median [IQR (Interquartile Range)], according to statistical distribution. Factors associated with hNa were studied using Chi-squared test or Fisher's exact test for categorical parameters, and Student's t-test or Mann-Whitney test for quantitative ones, as appropriate. The Gaussian distribution was verified by the Shapiro-Wilk test and homoscedasticity by the Fisher-Snedecor test. A multivariable analysis was implemented using a logistic regression, considering the covariates according to univariate results and clinical relevance. The results were expressed as odds-ratio (OR) and 95% confidence intervals (CI). In the subgroup of patients with hNa, the patients were compared according to the mineralocorticoids treatment (yes or no) with the same statistical tests.

## RESULTS

### DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Flowchart of the study is presented in **Figure 1**. Among the 773 patients with ICD-10 codes I60, I615 or G91 admitted between November 1<sup>st</sup>, 2012 and May 1<sup>st</sup>, 2020, 371 (48%) had aSAH. Of the 336 included aSAH patients, 102 (30%) presented hNa during the ICU stay.



**Figure 1.** Flowchart of the study

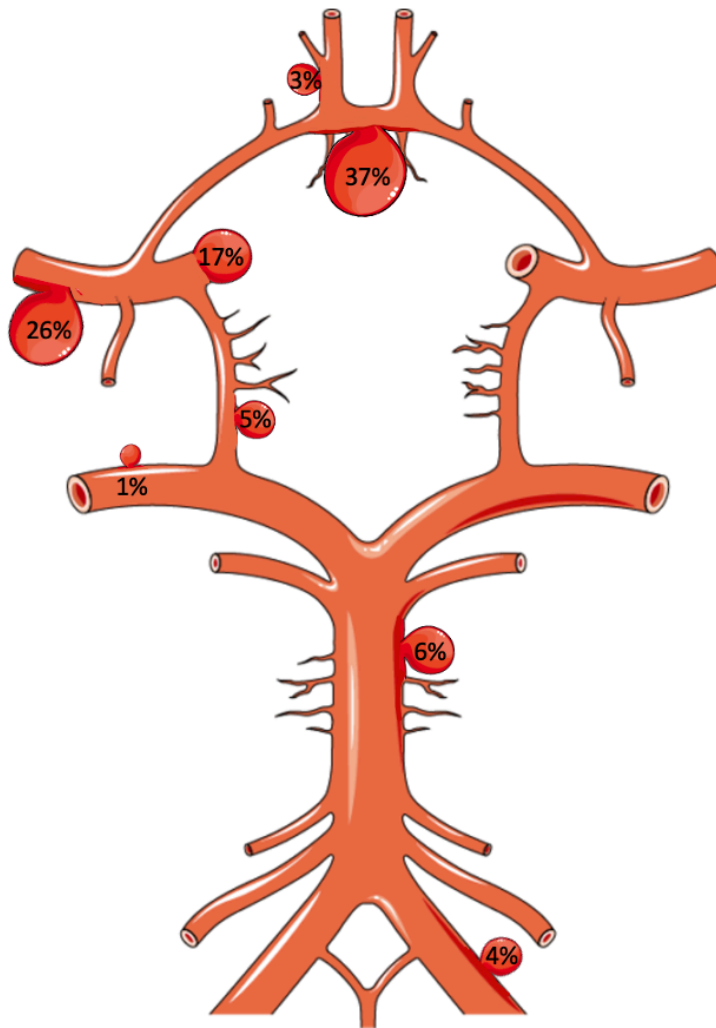
The demographic, clinical and biochemical characteristics of the patients are shown in **Table I**.

**Table I. Characteristics of the Study Patients**

	All patients (N=336)	Without hyponatremia (N=234)	With hyponatremia (N=102)	p value
Age, M ± SD	56 ± 14	57 ± 14	56 ± 13	0.60
Female sex, no. (%)	212 (63)	154 (66)	58 (57)	0.20
WFNS score, no. (%)				0.06
1	130 (39)	91 (39)	39 (38)	
2	59 (18)	32 (14)	27 (27)	
3	18 (5)	14 (6)	4 (4)	
4	58 (17)	44 (19)	14 (14)	
5	71 (21)	53 (23)	18 (18)	
rFischer scale, no. (%)				0.56
0	4 (1)	4 (2)	0 (0)	
1	59 (18)	40 (17)	19 (19)	
2	27 (8)	21 (9)	6 (6)	
3	109 (32)	78 (33)	31 (30)	
4	137 (41)	91 (39)	46 (45)	
Anterior circulation aneurysm, no. (%)	279 <sup>‡</sup> (83)	197 <sup>‡</sup> (84)	82 (80)	0.30
Anterior cerebral artery	11 (3)	6 (3)	5 (5)	
Anterior communicant artery	124 (37)	86 (37)	38 (37)	
Mean cerebral artery	87 (26)	66 (29)	21 (21)	
Internal carotid	57 (17)	39 (17)	18 (18)	
Posterior circulation aneurysm, no. (%)	55 <sup>‡</sup> (16)	35 <sup>‡</sup> (15)	20 (20)	0.30
Posterior cerebral artery	3 (1)	1 (0)	2 (2)	
Posterior communicant artery	17 (5)	12 (5)	5 (5)	
Basilar artery	21 (6)	14 (6)	7 (7)	
Vertebral artery	14 (4)	8 (4)	6 (6)	
Initial treatment, no. (%)				0.19
Surgical clipping	27 (8)	22 (9)	5 (5)	
Endovascular coiling	285 (85)	193 (83)	92 (90)	
No treatment	24 (7)	19 (8)	5 (5)	
Natremia at admission <sup>§</sup> , M ± SD	141 ± 3.5	141 ± 3.5	140 ± 3.5	< 0.01

*M = mean ; SD = Standard deviation ; WFNS = World Federation of Neurosurgical Societies ; rFischer = revisited Fischer's scale ; <sup>§</sup>mmol.L<sup>-1</sup> ; <sup>‡</sup>Missing data for 2p % may not equal 100 because of rounding*

Aneurysm site was anterior in 83% of SAH with no differences for the development of hyponatremia. The repartition of aneurysms sites is shown in **Figure 2**.



**Figure 2. Aneurysms locations in aSAH (336 patients)**

External ventricular drain was performed to treat hydrocephalus in 51% of aSAH. Admission natremia was lower in patients developing hNa during their ICU stay ( $140 \pm 3.5$  vs  $141 \pm 3.5$ ;  $p < 0.01$ ).

#### **HYPONATREMIA, aSAH THERAPIES AND OUTCOMES**

**Table II** shows outcomes and the univariate association between hNa and some aSAH therapies used during ICU management. hNa occurred at the 8<sup>th</sup> day ( $8 \pm 4.5$ ) after ictus. All hNa were hypotonic ( $272.4 \text{ mOsmol.L}^{-1} \pm 3.4$ ).

**Table II. Association between hyponatremia, therapies and outcomes**

	All patients (N=336)	Without hyponatremia (N=234)	With hyponatremia (N=102)	p value
<b>aSAH therapies</b>				
Osmotherapy, no. (%)	42 (13)	33 (14)	9 (9)	0.18
MAP target <sup>§</sup> , M ± SD	71.7 ± 9.8	70.6 ± 8.9	74.4 ± 11.3	< 0.05
Milrinone, no. (%)	117 (35)	70 (30)	47 (46)	< 0.01
Natriuretics, no. (%)	82 (24)	66 (28)	16 (16)	0.01
<b>Outcomes</b>				
Vasospasm, no. (%)	142 (42)	81 (35)	61 (51)	< 0.01
Delayed cerebral ischemia, no. (%)	76 (23)	42 (18)	34 (33)	< 0.01
ICU LOS, median [IQR]	12 [6;21]	10 [5;21]	16 [9;23]	< 0.01
Hospital LOS, median [IQR]	23 [16;38]	22 [16;35]	26 [18;42]	< 0.05
GOS 3 <sup>rd</sup> month, median [IQR] <sup>€</sup>	4 [3;5]	4 [1;5]	4 [3;5]	0.36
Mortality at 1 year, no. (%) <sup>£</sup>	73 <sup>£</sup> (27)	60 <sup>£</sup> (30)	13 <sup>£</sup> (18)	< 0.05

M = mean ; SD = Standard deviation ; MAP = Mean Arterial Pressure ; <sup>§</sup>mmHg ; LOS = Length Of Stay (days) ; IQR = Interquartile range  
<sup>€</sup>Missing data for 34 patients ; <sup>£</sup>Missing data for 64 patients. % may not equal 100 because of rounding

**MULTIVARIATE ANALYSIS**

Multivariate analysis was computed and results are presented in **Table III**. Low natremia at admission, a high target of mean arterial pressure (MAP) and vasospasm were independently associated with hNa. Diuretics (proximal and loop diuretics) were independently protectors of hNa.

**Table III. Criteria independently associated with hyponatremia**

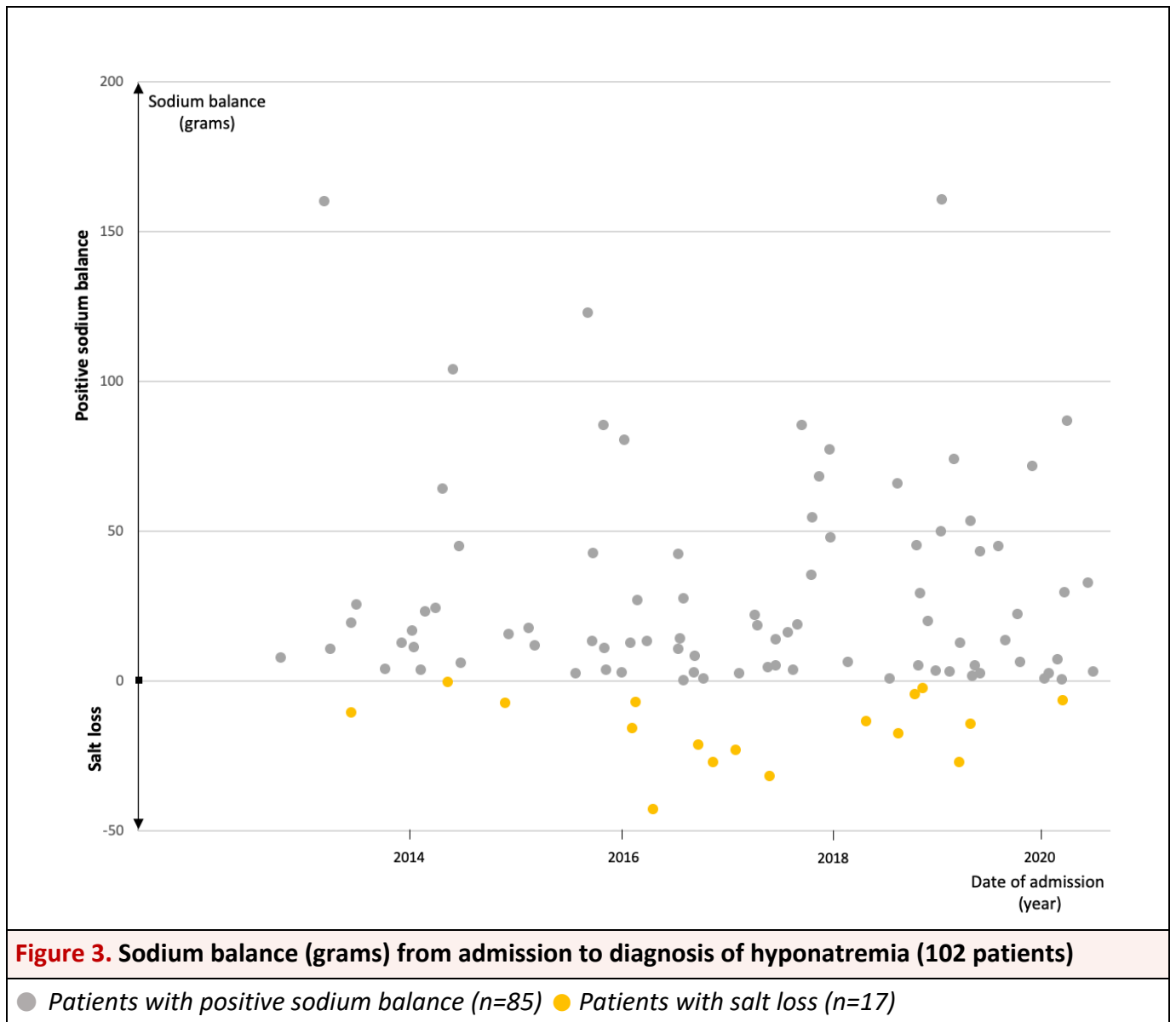
	Odds Ratio (95% CI)	p value
Natremia at admission	0.89 (0.82-0.96)	< 0.01
MAP target	1.03 (1.00-1.05)	0.03
Milrinone	0.79 (0.34-1.79)	0.57
Diuretics	0.41 (0.21-0.82)	0.01
Vasospasm	2.77 (1.20-6.38)	0.02
Delayed cerebral ischemia	1.75 (0.91-3.41)	0.10

MAP = Mean Arterial Pressure ; CI = Confidence Interval



### SALT LOSS IN PATIENTS WITH HYPONATREMIA

In patients with hNa (102 patients), sodium intakes from admission to diagnosis of hNa were  $105g \pm 80$  whereas sodium urinary loss were  $83g \pm 64$ . Sodium balance and salt loss status are presented in **Figure 3**.



Seventeen patients had salt loss (17% of hNa patients). Sodium intakes, sodium loss, hydric intakes and hydric loss are presented in **Table IV**. Among the 17 patients with salt loss, 12 (71%) had diagnosis compatible with ISW : 6 (35%) had milrinone, 4 (24%) had acetazolamide,

1 (6%) had ddAVP and 1 (6%) had more than  $5\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  of noradrenaline in the day preceding the diagnosis of hNa. Although only 17 patients had actually salt loss, CSW was evocated by physicians in 90 patients with hNa (88%). Salt supplementation was given by clinicians to all of those 90 patients.

**Table IV. Intakes and loss from admission to the day of hyponatremia**

	All patients (N=102)	Positive sodium balance (N=85)	Salt loss (N=17)	p value
Sodium intakes (g)	105 ± 80	108 ± 83	92 ± 58	0.36
Sodium loss (g)	83 ± 64	78 ± 64	108 ± 63	0.09
Hydrics intakes (L)	13.1 ± 11.2	13.4 ± 11.9	11.4 ± 7.3	0.35
Hydrics loss (L)	17.2 ± 14.0	16.9 ± 14.2	18.9 ± 13.2	0.57

*All results are Mean ± SD ; g = grams ; L = Liters*

Biochemical characteristics of patients with hNa are summarized in **Table V**. No statistically significant differences existed in plasma sodium, osmolarity, plasma urea and urine volume the day of diagnosis of hNa between patients with positive sodium balance and patients with salt loss. Natriuresis was significantly increased in patients with salt loss.

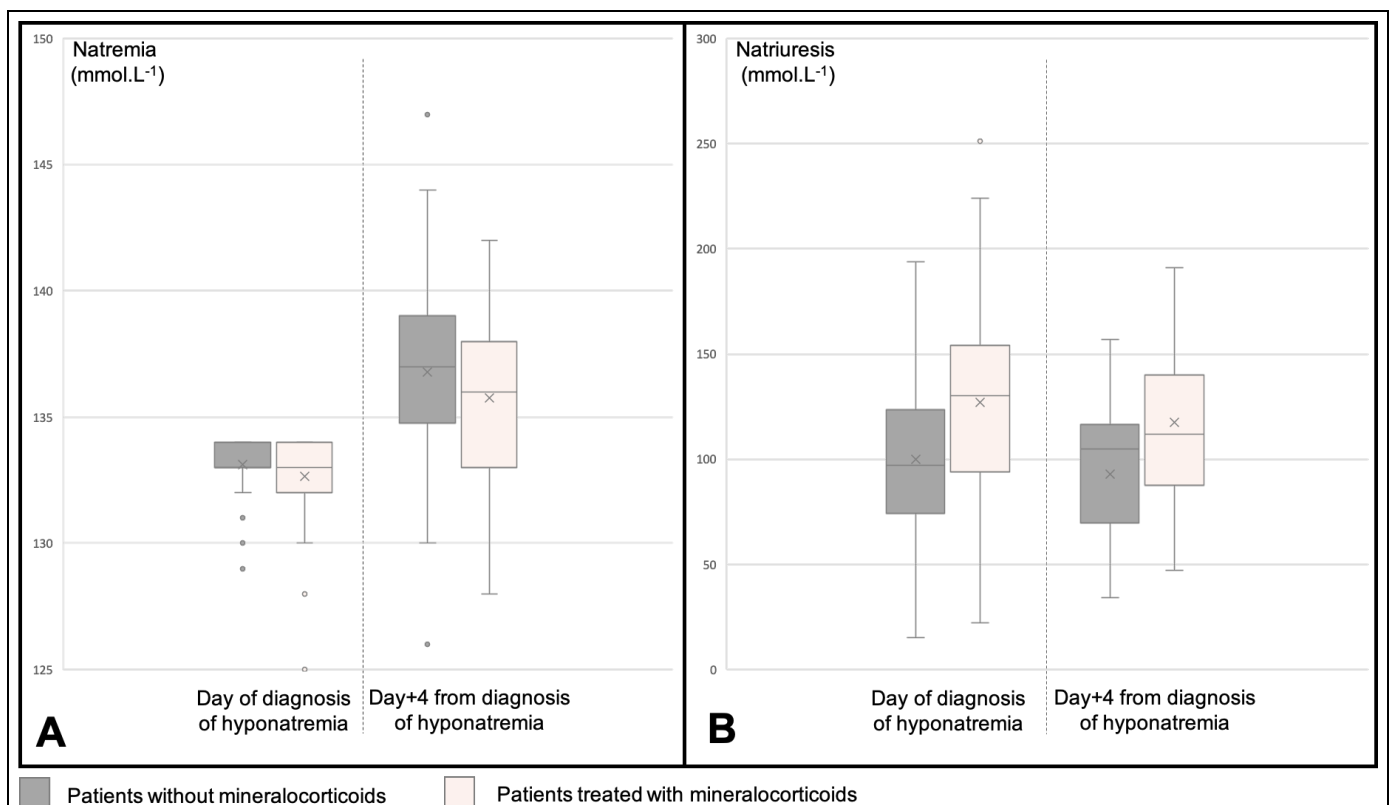
**Table V. Biochemical characteristics at diagnosis of hyponatremia in aSAH**

	All patients (N=102)	Positive sodium balance (N=85)	Salt loss (N=17)	p value
Plasma sodium ( $\text{mmol}\cdot\text{L}^{-1}$ ) <sup>£</sup>	132.9 ± 3.9	131.6 ± 2.7	132.4 ± 3.3	0.27
Plasma osmolarity ( $\text{mOsmol}\cdot\text{L}^{-1}$ ) <sup>£</sup>	272.4 ± 3.4	272.5 ± 3.4	271.9 ± 3.3	0.50
Plasma urea ( $\text{mmol}\cdot\text{L}^{-1}$ ) <sup>£</sup>	5.0 ± 2.7	5.1 ± 2.7	4.6 ± 2.4	0.45
Urine volume ( $\text{L}\cdot\text{d}^{-1}$ ) <sup>£</sup>	2.9 ± 1.5	2.87 ± 1.6	3.1 ± 1.1	0.53
Natriuresis ( $\text{mmol}\cdot\text{L}^{-1}$ ) <sup>£</sup>	114.6 ± 46.4	110.1 ± 47.1	137.2 ± 35.7	0.01

*All results are Mean ± SD ; L.d<sup>-1</sup> = Liters per day ; <sup>£</sup>Day of the diagnosis of hyponatremia*

## IMPACT OF MINERALOCORTICOIDS IN HYPONATREMIC PATIENTS

In patients with hNa, mineralocorticoids treatment was introduced in 55/102 patients (54%) regardless the mechanism of hNa. Fludrocortisone acetate was the mineralocorticoid of choice for 52/55 patients (95%). Dosages ranged from 50 $\mu$ g/day to 300 $\mu$ g/day. In comparison to others, patients with mineralocorticoids did not improve their natremia and natriuresis 4 days after diagnosis of hNa as shown in **Figure 4**.



**Figure 4. Evolution of natremia (A) and natriuresis (B) in hNa patients with or without mineralocorticoids**

Box plots : median (—), mean (x), interquartile range (□), minimum (⊥), maximum (⊤) and outliers (•)

There were no differences in complications (vasospasm, DCI), in ICU and hospital length of stay, in neurological outcomes (GOS at 3<sup>rd</sup> month) and mortality rate at 1 year between patients receiving mineralocorticoids agents and those who didn't as shown in **Table VI**.

**Table VI. Outcomes of hNa patients treated with mineralocorticoids**

	All patients (N=102)	No mineralo -corticoids (N=47)	Mineralo -corticoids (N=55)	p value
Vasospasm, no. (%)	61 (60)	26 (55)	35 (64)	0.39
DCI, no. (%)	34 (33)	20 (43)	14 (25)	0.07
ICU LOS, median [IQR]	16 [9;23]	16 [8;25]	15 [10;22]	0.79
Hospital LOS, median [IQR]	26 [18;42]	25 [18;44]	26 [17;38]	0.81
GOS 3 <sup>rd</sup> month <sup>§</sup> , median [IQR]	4 [3;5]	4 [3;5]	4 [3;5]	0.80
Mortality at 1 year <sup>§</sup> , no. (%)	13 (18)	7 (19)	6 (16)	0.68

*DCI = Delayed cerebral ischemia ; GOS = Glasgow Outcome Scale ; LOS = Length Of Stay (days) ; IQR = Interquartile Range.*

*<sup>§</sup>Data were missing for 12 patients (GOS) and 28 patients (Mortality)*

## DISCUSSION

Our cohort exploring incidence and pathophysiology of hNa in aSAH patients is one of the biggest published (5,10,12,13,27,28). Salt loss was rare (17% of aSAH patients with hNa). Only 5/102 patients (5%) had no ISW and could have a syndrome compatible with CSW. However, CSW was suspected and treated in almost all cases (88%) of hNa. These results contrast with smaller studies (29-31) but are in accordance with Sherlock et al. and Brimiouille et al. whose data didn't support the concept of CSW in hNa complicating aSAH. (12,32) There is no objective criteria to diagnose CSW with a consensual definition. Its evocation depends on the clinical presentation and especially clinician's assessment of blood volume. We provide an objective method to measure sodium balance, that allows the physicians to eliminate the diagnosis of CSW in the absence of salt loss. Among patients with salt loss, however, it is necessary to define whether the syndrome can be included in CSW or not by eliminating ISW. Finally, an idiopathic salt loss after aSAH could be considered from cerebral origin and define the CSW.

Thirty percent of aSAH patients developed hNa during their ICU stay. Natremia at the admission was significantly lower in patients who developed hNa. Previous studies have reported a high incidence of hNa in aSAH secondary to rupture of anterior communicating artery aneurysm. (33) In our cohort there was no difference between aneurysms location in the development of hyponatremia.

According to our data, hNa was associated with more vasospasm. There was no increase of mortality, in agreement with previous studies. (12,34) A high MAP target was independently at risk for development of hNa. This could be due to increased renal perfusion or increased use of catecholamines. Diuretics were protective factors for hNa, suggesting that the mechanism of hNa is more related to dilutional hNa than to salt loss.

In our cohort, mineralocorticoids did not improve natremia or natriuresis after 4 days from the diagnosis of hNa. Other studies showed no impact in the first 7 days of treatment. (35-37) Mineralocorticoids failed to improve vasospasm rate, DCI, hospital length of stay, GOS at 3<sup>rd</sup> month and mortality rate at 1 year. These data suggest that anti-natriuretic effect of mineralocorticoids is not effective to treat hNa complicating aSAH and do not support the concept of hypernatremia leading to CSW.

Our study has some limitations. First, due to pathophysiological aspects, we excluded patients with hNa at admission. Some cases had incomplete documentation of clinical history and laboratory testings. TSH and cortisol exploration were not systematic at the diagnosis of hNa. We did not have full access to fluids volume used during endovascular coiling or surgical clipping and thus we may have overestimated patients with salt loss. Even if rare, we could not exclude hNa occurring after ICU stay. Central venous pressure, that could be a surrogate of volemic status and urine osmolality were rarely monitored and could not be evaluated in our cohort.

In conclusion, hNa is common following aSAH and appears in the first ten days after ictus. Salt loss represents a rare mechanism leading to hNa and was attributable to CSW in few patients. These data suggest that CSW must be considered as a rare cause of hNa post aSAH and that mineralocorticoids are ineffective in this indication. A large prospective study on salt wasting and mineralocorticoids agents in patients with aSAH is needed to confirm these data.

Le Doyen de l'UFR de Médecine,

Pr Pierre CLAVELOU



Le Président du Jury,

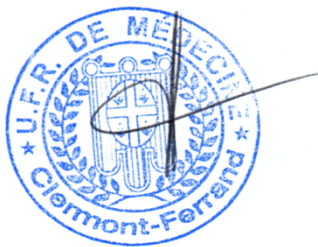
Pr Jean-Etienne BAZIN

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En conclusion, l'hyponatrémie (hNa) est fréquente et apparaît dans les 10 jours après une hémorragie sous-arachnoïdienne anévrysmale (aHSA). La perte en sel était un mécanisme rare menant à l'hNa post aHSA et était attribuable au syndrome de perte en sel d'origine cérébrale (CSW) chez seulement quelques patients. Ces données suggèrent que le CSW doit être considéré comme une cause rare d'hNa post aHSA et que les agents minéralocorticoïdes sont inefficaces dans cette indication. Une étude prospective sur la perte en sel et sur l'effet des minéralocorticoïdes chez les patients présentant une aHSA est nécessaire à la confirmation de ces résultats.

Le Doyen de l'UFR de Médecine,

Pr Pierre CLAVELOU



Le Président du Jury,

Pr Jean-Etienne BAZIN

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## ABSTRACT

**INTRODUCTION :** In aneurysmal subarachnoid hemorrhage (aSAH), hyponatremia (hNa) is related to inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting syndrome (CSW). In clinical practice, distinction between the two conditions is difficult but critical since treatments are fundamentally different. Notably, diagnostic criteria of CSW are touchy and CSW incidence is unclear.

**ENDPOINTS :** The primary endpoint was the measure of salt loss in hNa patients to assess incidence of CSW in aSAH. Secondary end points were the evaluation of 1 year mortality and neurological outcomes in hNa patients with or without salt loss. Effect of mineralocorticoid treatment in hNa was also analysed.

**METHODS :** We conducted a retrospective monocentric study and included consecutive aSAH patients between November 1<sup>st</sup>, 2012, and May 1<sup>st</sup>, 2020. Exclusion criteria were hNa on the day of hospitalization and a history of severe renal failure, congestive heart failure and unstable endocrine disorders.

**RESULTS :** Of the 336 included aSAH patients, 102 (30%) presented hNa during the ICU stay. Seventeen patients had salt loss (17% of hNa patients) and 5 were attributable to CSW (5%). CSW was diagnosed by physicians in 90 patients with hNa (88%) and salt supplementation was given to all of those 90 patients. In hNa patients, sodium intakes were  $105.2\text{g} \pm 79.6$  and salt loss was  $83.3\text{g} \pm 64.4$ . Mortality at 1 year, Glasgow Outcome Scale at 3<sup>rd</sup> month, natremia at 4 days, natriuresis at 4 days and vasospasm were similar in patients treated by mineralocorticoids or not.

**CONCLUSION :** Salt loss represents a rare mechanism leading to hNa and could attributable to CSW in few cases. Our data suggest that CSW must be considered as a rare cause of hNa post aSAH and that mineralocorticoids are ineffective in this indication.

## SERMENT D'HIPPOCRATE (Conseil national de l'ordre des médecins)

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Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.

Pierre-Antoine Pioche



## SERMENT D'HIPPOCRATE

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En présence des Maîtres de cette FACULTÉ et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

Pierre-Antoine Pioche

A handwritten signature in black ink, consisting of a series of loops and a long horizontal stroke extending to the right.

## RESUME DE LA THESE

### Hyponatrémie et hémorragie sous-arachnoïdienne anévrysmale : existe-t-il une perte en sel ?

#### RESUME :

**INTRODUCTION :** Le syndrome de perte en sel d'origine cérébrale (anglais, CSW) est une des deux causes principales d'hyponatrémie (hNa) compliquant les hémorragies sous-arachnoïdiennes anévrysmales (anglais, aSAH). Les évaluations permettant de le différencier d'un syndrome d'antidiurèse inappropriée (anglais, SIADH) sont difficiles et la prise en charge de ces deux syndromes est opposée.

**OBJECTIFS :** L'objectif principal de l'étude était la mesure de la perte en sel chez les patients présentant une hNa secondaire à une aSAH et d'estimer la fréquence du CSW. Les objectifs secondaires comprenaient l'évaluation de la mortalité à 1 an, du handicap neurologique à 3 mois et des complications neurologiques chez les patients présentant une hNa avec ou sans perte en sel. Les effets des traitements minéralocorticoïdes dans l'hNa étaient aussi analysés.

**METHODES :** Il s'agit d'une étude rétrospective monocentrique incluant les patients admis en réanimation pour une aSAH entre le 1/11/2012 et le 1/05/2020. Les patients présentant une hNa à l'admission, une insuffisance rénale sévère ou une endocrinopathie décompensée étaient exclus. La perte en sel était définie par une perte en sel urinaire supérieure aux apports mesurés entre l'admission et le diagnostic de l'hNa et était nécessaire au diagnostic de CSW.

**RESULTATS :** Trois cents trente-six patients ont été inclus. Parmi les 102 patients (30%) qui ont présenté une hyponatrémie, 17 (17%) avaient une perte en sel ( $16,0g \pm 11,6$ ) et seulement 5 (5%) étaient compatibles avec un CSW. Ce syndrome était pourtant suspecté et traité par les cliniciens dans 88% des hNa (90/102). Parmi les 102 patients, les apports sodés étaient en moyenne de  $105,2 \pm 79,6g$  et la perte urinaire de  $83,3 \pm 64,4g$ . La mortalité à 1 an (19% vs 16%,  $p = 0,68$ ), le score GOS à 3 mois (4 [3 ;5] vs 4 [3 ;5],  $p = 0,80$ ), la natrémie à J4, la natriurèse à J4 et le taux de vasospasme étaient semblables dans le groupe traité par minéralocorticoïdes ou non.

**CONCLUSION :** La perte en sel permet d'expliquer la physiopathologie de l'hyponatrémie dans l'HSA anévrysmale dans moins de 5% des cas. Le traitement anti-natriurétique par minéralocorticoïdes n'a pas montré de bénéfice sur la correction de la natrémie, la survie et le handicap neurologique. Ces données suggèrent que le CSW devrait être considéré comme un diagnostic d'exception.

**MOTS-CLES:** subarachnoid hemorrhage, hyponatremia, inappropriate ADH syndrome, cerebral salt wasting, fludrocortisone acetate

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