Association of copeptin, a surrogate marker of arginine vasopressin, with cerebral vasospasm and delayed ischemic neurologic deficit after aneurysmal subarachnoid hemorrhage

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OBJECTIVE Delayed ischemic neurological deficit (DIND) is a leading cause of mortality and morbidity after aneurysmal subarachnoid hemorrhage (aSAH). Arginine vasopressin (AVP) is a hormone released by the posterior pituitary. It is known to cause cerebral vasoconstriction and has been implicated in hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion. Direct measurement of AVP is limited by its short half-life. Copeptin, a cleavage product of the AVP precursor protein, was therefore used as a surrogate marker for AVP. This study aimed to investigate the temporal relationship between changes in copeptin concentrations and episodes of DIND and hyponatremia.

METHODS Copeptin concentrations in cerebrospinal fluid were quantified using enzyme-linked immunosorbent assay in 19 patients: 10 patients with DIND, 6 patients without DIND (no-DIND), and 3 controls.

RESULTS Copeptin concentrations were higher in DIND and no-DIND patients than in controls. In hyponatremic DIND patients, copeptin concentrations were higher compared with hyponatremic no-DIND patients. DIND was associated with a combination of decreasing sodium levels and increasing copeptin concentrations.

CONCLUSIONS Increased AVP may be the unifying factor explaining the co-occurrence of hyponatremia and DIND. Future studies are indicated to investigate this relationship and the therapeutic utility of AVP antagonists in the clinical setting.

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KEYWORDS arginine vasopressin; cerebral vasospasm; copeptin; delayed ischemic neurologic deficit; hyponatremia; syndrome of inappropriate antidiuretic hormone secretion; vascular disorders

DELAYED ischemic neurological deficit (DIND) is a major cause of mortality and morbidity, with 15%–20% of patients suffering a stroke or dying despite maximal therapeutic intervention.⁴ DINDs occur with the greatest frequency 7–10 days following aneurysmal rupture.⁹ Cerebral vasospasm (CVS) is no longer viewed as the main determinant of DIND due to increasing preclinical and clinical evidence that multiple factors contribute to DIND, including microvascular constriction, micro-

thrombosis, cortical spreading ischemia, inflammation, blood-brain barrier disruption, electrolyte disturbances, mechanical injury and cerebral autoregulation disruption, excitotoxicity, nitric oxide alterations and endothelin-1 increase, oxidative stress, and apoptosis.^{6,8,10,18,19,28}

Numerous investigations have been undertaken to identify biomarkers that could predict the development of DIND and serve as potential therapeutic targets.^{2,17,23,24} However, currently it is still not possible to reliably predict

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; AVP = arginine vasopressin; CSF = cerebrospinal fluid; CVP = central venous pressure; CVS = cerebral vasospasm; DIND = delayed ischemic neurological deficit; DSA = digital subtraction angiography; ELISA = enzyme-linked immunosorbent assay; ICU = intensive care unit; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

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the incidence and timing of episodes of DIND in individuals who have suffered an aneurysmal subarachnoid hemorrhage (aSAH).^{17,24}

Arginine vasopressin (AVP), otherwise known as antidiuretic hormone, is a peptide which is synthesized in the hypothalamus and released into the bloodstream by the posterior pituitary.^{11,21} It is known to cause systemic and cerebral vasoconstriction via action on V_1 receptors, and maintain systemic fluid and electrolyte balance through promotion of water reabsorption via renal V_2 receptors.^{12,15}

In syndrome of inappropriate antidiuretic hormone secretion (SIADH), however, excessive AVP secretion causes water retention, which leads to dilutional hyponatremia.²⁶ Several studies have demonstrated an association between hyponatremia and DIND,^{14,27,29} and severe hyponatremia and DIND can present with similar clinical symptoms, such as mental status changes.²⁶

A significant difficulty encountered in measuring AVP directly is its short half-life.¹ In contrast, copeptin, a cleavage product of the AVP precursor protein, has high stability *ex vivo* and is released in equimolar concentrations,¹ with various studies establishing that copeptin levels accurately mirror AVP levels.^{3,5,11,16} Measurement of copeptin is easily performed using manual or wholly automated chemiluminescence assays.¹¹ As such, we chose to use copeptin as a surrogate marker for AVP.

To date, the temporal pattern of copeptin in cerebrospinal fluid (CSF) after aSAH is not known since copeptin levels have only been measured in plasma at the singular time point of admission following aSAH.^{13,31} We hypothesized that the occurrence of episodes of DIND and hyponatremia after aSAH would be associated with increased copeptin concentrations. Therefore, the aim of this study was to investigate the temporal relationship between changes in copeptin levels in CSF following aSAH and the occurrence of DIND and hyponatremia.

Methods

Patient Population and Classification

This study was performed using patient information collected as part of an ongoing prospective database of clinical, biochemical, and radiological data from patients with confirmed aSAH. Exclusion criteria were presentation with traumatic SAH, a diagnosed arteriovenous malformation, or presence of a ventriculoperitoneal shunt. Written informed consent was obtained from all patients or their next of kin. The Melbourne Health Human Research Ethics Committee, which is governed by the guidelines of the National Health and Medical Research Council, approved this study.

Patients with aSAH presenting with symptoms that raised clinical suspicion of DIND and who were confirmed to have radiological CVS on digital subtraction angiography (DSA) were assigned to the DIND group. Patients who did not present with symptoms suggestive of DIND were assigned to the without DIND (no-DIND) group. Patients who presented with clinical suspicion of aSAH but were confirmed not to have a hemorrhage by CT brain scan and lumbar puncture were classified as controls.

Patient Management

The diagnosis of SAH was established using CT brain scanning or by the presence of blood/xanthochromia in the CSF collected via lumbar puncture. Symptomatic hydrocephalus was treated with insertion of a ventriculostomy catheter and drainage of CSF at the discretion of the treating neurosurgeon. All patients underwent cerebral DSA for identification of aneurysm location and morphology. All aneurysms were secured by either endovascular coiling or microsurgical clipping within 24 hours of admission. Clinically significant intracerebral hematomas were evacuated. Postoperatively, patients were extubated and managed at a neurosurgical high-dependency unit unless they required mechanical ventilation or inotropic support, in which case they were managed in the intensive care unit (ICU).

All patients had a central venous catheter (internal jugular or subclavian) inserted and were given supplementary fluids to maintain mild hypervolemia and a central venous pressure (CVP) target of > 8 cm H_2O . All patients were administered prophylactic nimodipine (oral or intravenous) from admission and for 21 days posthemorrhage. Patients received mechanical thromboembolic prophylaxis and were mobilized early. Fever was treated with paracetamol administration and noninvasive cooling. Blood transfusions were given to maintain hemoglobin levels > 8 mg/dl. Clinically significant hyponatremia was treated with the administration of hypertonic saline infusion (3% saline) at the discretion of the treating neurosurgeon and intensivist. Serum potassium and magnesium levels were maintained within the normal range.

Anticonvulsant agents were administered if there was evidence of seizure activity or prophylactically at the time of craniotomy and for a variable period thereafter according to the treating neurosurgeon. Hypertensive therapy was not initiated routinely but only after the diagnosis of DIND.

Patients suspected of developing DIND who had a CVP < 8 cm H_2O were immediately given a fluid bolus (0.9% saline) to restore CVP > 8 cm H_2O . If they remained symptomatic, hypertensive therapy was initiated using a noradrenaline infusion targeting a systolic blood pressure of up to 200 mm Hg or until reversal of the neurological deficit. A CT brain scan was acquired to exclude other causes of deterioration or an established infarct, and hypertensive therapy was continued in the ICU, aiming to maintain the lowest possible systolic blood pressure at which the patient remained deficit free. CVS was confirmed with cerebral angiography and in selected patients who remained symptomatic despite hypertensive therapy. Balloon angioplasty or administration of intraarterial nimodipine or verapamil was used at the discretion of the endovascular neuroradiologist and treating neurosurgeon. Vasopressin infusion was not used to induce hypertension in any of the patients included in this study.

Collection and Storage of CSF

In aSAH patients, CSF was collected prospectively every 24 hours, when practicable, from an extraventricular drain and via lumbar puncture from controls. To eliminate the potential influence of diurnal variation on AVP, CSF

samples were primarily collected in the morning. At each collection, CSF was obtained in a 10-ml cryogenic tube using aseptic technique, followed by immediate storage in a refrigerator at 4°C at the Royal Melbourne Hospital. Most samples were centrifuged on the day of collection (2500g for 5 minutes). One-milliliter aliquots of CSF were prepared and labeled with the respective patient number and days of collection. Aliquots were stored at -80°C in a locked freezer.

CSF Analysis

CSF samples were transferred from Royal Melbourne Hospital in a styrofoam box filled with dry ice to a -80°C freezer at the University of Melbourne Department of Pharmacology and Therapeutics on the day prior to testing. CSF analysis was conducted using a Human Copeptin ELISA kit CUSABIO, which utilizes a quantitative sandwich enzyme immunoassay technique. The detection range of the kit is 78–5000 pg/ml. The minimum concentration of human copeptin that can be detected is cited as typically less than 19.5 pg/ml. This assay was selected for its high sensitivity and specificity.

As part of the enzyme-linked immunosorbent assay (ELISA) protocol, a 1:2 dilution of the reconstituted standard was performed using sample diluent. One-milliliter aliquots of CSF samples to be analyzed were thawed on the day of testing. We added 50 µl of CSF to 450 µl of Milli-Q H₂O, resulting in a 1:10 dilution of CSF. The standards and samples were added to the wells of a microplate that had been precoated with antibody specific for copeptin, followed by incubation for 2 hours at 37°C. Both standards and samples were plated in duplicate. After the removal of any unbound material, a biotin-conjugated antibody specific for copeptin was added, and incubation took place at 37°C for 1 hour. The wells were then washed (3 × 200 µl wash buffer), and avidin-conjugated horseradish peroxidase was added, followed by incubation at 37°C for 1 hour. A second washing step (5 × 200 µl wash buffer) was carried out to remove any unbound avidin-enzyme reagent, and 90 µl of tetramethylbenzidine substrate solution was added, which produced color development that was proportionate to the amount of copeptin bound in the previous step. Color development was stopped using 50 µl of stop solution, and absorbance at 450 nm was measured with a spectrophotometer using Ascent Software version 2.6.

The duplicate absorbance readings for each standard and CSF sample were averaged. A linear standard curve was produced by plotting the log of copeptin concentrations versus the log of absorbance of the standards and drawing a line of best fit. Concentrations read off this curve were multiplied by the dilution factor of 10 to obtain the copeptin concentration of each CSF sample.

Experimental Design

Experiments were designed to determine the temporal pattern of copeptin from the day of aSAH to the day of DIND onset. Copeptin concentrations were analyzed 1–10 days post-aSAH, since this includes the typical time frame in which DIND occurs. When CSF samples for days 1, 4, 6, 8, and 10 post-aSAH were available, these were tested.

Otherwise, samples from the day after were analyzed. The temporal pattern of copeptin post-aSAH was determined in 6 DIND and 6 no-DIND patients, and the mean copeptin for each day post-aSAH was calculated. Copeptin was also measured in 3 control patients. For a patient who had the unique occurrence of two episodes of DIND, all available CSF samples post-aSAH were tested. The temporal pattern of copeptin was also defined 6 days before and after the day of DIND onset in the initial group of 6 DIND patients and 3 additional DIND patients. The mean copeptin level for each day was determined.

For all the days that CSF was tested, serum sodium values were collated from electronic patient records of blood gas measurements and electrolyte levels. The mean sodium for each day was calculated and days on which hyponatremia (defined as mean serum sodium < 135 mmol/L) occurred were noted. Copeptin concentrations were matched with the mean serum sodium values obtained for the respective days. A retrospective review of patient ICU and ward records was also conducted to determine whether an AVP infusion or desmopressin was administered on the days that CSF was tested.

Statistical Analysis

Data analysis was performed using GraphPad Prism version 6.0. Nonparametric tests were used to compare the copeptin concentrations of DIND and no-DIND patients because the data did not have a normal distribution. Two-way ANOVA was performed on the copeptin concentrations of DIND patients measured 1–10 days post-aSAH, followed by a post hoc Tukey's test. This was because we were interested in examining the interaction between two independent variables: the day of DIND occurrence post-aSAH and the copeptin concentration. One-way ANOVA was performed when comparing copeptin concentrations of hyponatremic DIND and hyponatremic no-DIND patients since the aim was to assess the effect of the single variable of hyponatremia on copeptin levels. A *p* value < 0.05 was taken to indicate statistical significance. Mean values are presented ± SD.

Results

Nineteen patients (13 women and 6 men) were included in the study. Patient demographics are presented in Table 1. There were 10 DIND patients, 6 no-DIND patients, and 3 control patients. The mean age of the patients was 57 ± 15 (range 26–86 years). The majority of aSAH patients were female (11/16), and the most common ruptured aneurysm site was the anterior communicating artery (6/16). The mean day of DIND occurrence post-aSAH was day 10 (Table 1).

Copeptin was detected in the CSF of all patients. The three control patients had a mean CSF copeptin level of only 253 ± 24 pg/ml, whereas the mean CSF copeptin levels 1–2 days after aSAH was 20- to 25-fold higher. Mean day 1–2 copeptin was 5320 ± 1881 pg/ml (*n* = 6) in no-DIND patients and 6992 ± 1763 pg/ml (*n* = 6) in the DIND patients. These early (day 1–2) post-aSAH copeptin levels did not differ between the no-DIND and DIND patients (*p* > 0.05, *t*-test). In contrast, a temporal analysis indicated

TABLE 1. Patient demographics

Pt No.	DIND/No-DIND/Control	Sex	Age (yrs)	Modified Fisher Grade	WFNS Grade	Day of Cerebral Vasospasm Post-aSAH	Site of CSF Acquisition	Ruptured Aneurysm Site
1	DIND	F	60	4	II	1) Day 9, 2) day 18	EVD	Basilar tip
2	DIND	F	51	4	II	Day 9	EVD	Anterior communicating artery
3	DIND	F	36	2	II	Day 4	EVD	Anterior communicating artery
4	DIND	F	86	3	I	Day 10	EVD	Anterior communicating artery
5	DIND	F	76	3	II	Day 8	EVD	Posterior communicating artery
6	DIND	M	63	3	IV	Day 7	EVD	Middle cerebral artery (mycotic)
7	DIND	F	59	4	IV	Day 7	EVD	Posterior communicating artery
8	DIND	F	50	4	IV	Day 8	EVD	Anterior communicating artery
9	DIND	F	54	4	I	Day 10	EVD	Posterior communicating artery
10	DIND	M	61	4	III	Day 16	EVD	Left superior cerebellar artery
11	No-DIND	M	62	3	V	NA	EVD	Basilar tip
12	No-DIND	M	50	2	V	NA	EVD	Anterior communicating artery
13	No-DIND	F	40	4	V	NA	EVD	Middle cerebral artery
14	No-DIND	M	54	2	III	NA	EVD	Anterior communicating artery
15	No-DIND	F	82	4	II	NA	EVD	Left ophthalmic artery
16	No-DIND	F	68	1	II	NA	EVD	Middle cerebral artery
17	Control	F	26	NA	NA	NA	LP	NA
18	Control	F	43	NA	NA	NA	LP	NA
19	Control	M	71	NA	NA	NA	LP	NA

EVD = extraventricular drain; LP = lumbar puncture; NA = not applicable; Pt = patient; WFNS = World Federation of Neurosurgical Societies.

that in no-DIND patients copeptin concentrations rose slightly on day 3–4 post-aSAH and then returned to the initial levels, whereas in the DIND patients, copeptin levels continued to rise, peaking at $16,392 \pm 8952$ pg/ml ($n = 3$) on days 9–10 (Fig. 1). Analysis indicated a statistically significant difference in copeptin concentrations on days 8–9 and 10 in DIND patients, compared with days 1–2 ($p < 0.05$, two-way ANOVA) (Fig. 1). In matched samples of DIND and no-DIND patients according to day after aSAH and for up to 10 days post-aSAH, the mean copeptin levels were higher in DIND patients ($14,418 \pm 2405$ pg/ml)

FIG. 1. The temporal pattern of copeptin in DIND and no-DIND (nDIND) patients 1–10 days after aSAH. In no-DIND patients ($n = 6$), copeptin levels peaked on days 4–5 and then decreased. This contrasted with DIND patients ($n = 6$), in whom copeptin levels continued to rise on days 6–10 post-aSAH. A nonparametric two-way ANOVA indicated a statistically significant difference ($p < 0.05$) between copeptin levels on DIND days 8–9 and day 10 compared with DIND days 1–2.

compared with no-DIND patients ($10,111 \pm 2773$ pg/ml) ($p < 0.05$, t-test).

Figure 2A shows daily matched CSF copeptin and serum sodium values from a single patient who had two episodes of DIND. The first episode occurred during a period of rising copeptin and falling sodium and was treated successfully with hypertensive therapy and balloon angioplasty. The second episode of DIND occurred during a period of hyponatremia that was being treated with administration of 3% saline.

When the serum sodium and CSF copeptin data from DIND patients were plotted relative to the day of DIND onset, there was a pattern of increasing copeptin and falling serum sodium leading up to the day of DIND onset (Fig. 2B).

When copeptin concentrations were matched with the mean sodium values obtained for the respective days, hyponatremic DIND patients were found to have higher copeptin values than hyponatremic no-DIND patients ($p < 0.05$, one-way ANOVA) (Fig. 3).

Discussion

The main findings from this study are as follows: 1) CSF copeptin levels in DIND patients continued to rise on days 6–10 after aSAH, whereas in no-DIND patients, CSF copeptin peaked on days 4–5 and then decreased; 2) increased CSF copeptin levels were associated with a hyponatremic state in the DIND patients; and 3) a combination of falling serum sodium levels and increasing CSF copeptin concentrations was associated with the occurrence of DIND.

A

B

FIG. 2. A: Copeptin and sodium levels of a patient with two episodes of DIND. The first episode of DIND (day 9) occurred during a period of rising copeptin and falling sodium. The second episode of DIND (day 18) occurred during a period of hyponatremia being treated with 3% saline. **B:** The temporal pattern of copeptin and sodium relative to day of DIND. The mean copeptin and sodium levels of 9 DIND patients 6 days before and after the day of DIND are shown. A combination of falling sodium levels and increasing copeptin concentrations was associated with the occurrence of DIND.

Copeptin Differences Between DIND and No-DIND Groups

Greater differences between the copeptin concentrations of DIND and no-DIND patients started to occur from days 6–7 after aSAH, with the most significant difference observed 10 days after aSAH. Importantly, this correlates with the 7- to 10-day time frame during which DIND occurs with the greatest frequency after aneurysm rupture.⁹ AVP has been shown to play a significant role in the inflammatory response to brain injury.²⁵ Since copeptin is a marker of AVP, this could indicate that ongoing inflammation contributes to the development of DIND.

The Predictive Value of Copeptin

Copeptin may have value as a predictor of DIND because a progressive increase in CSF copeptin was observed in the days leading up to DIND onset (Fig. 2B). Although formal analysis of the predictive value in terms

FIG. 3. Higher copeptin levels in hyponatremic DIND patients compared with hyponatremic no-DIND patients. Copeptin concentrations were matched with the mean serum sodium values obtained for the respective days. Hyponatremic DIND patients ($n = 7$) had higher copeptin concentrations than hyponatremic no-DIND patients ($n = 6$). *A nonparametric one-way ANOVA indicated a statistically significant difference ($p < 0.05$) between copeptin concentrations in hyponatremic DIND patients compared with hyponatremic no-DIND patients.

of sensitivity and specificity was not carried out, a change in CSF copeptin levels within this time frame indicating that DIND is imminent would allow for prophylactic escalation of therapy. The predictive value of copeptin could potentially be increased if included as a component of a panel of predictive biomarkers.²³

Determining if AVP Elevation Causes DIND

Establishing whether increased copeptin concentrations (and in effect AVP) precede the development of DIND is crucial in establishing causation. Due to substantial intra-individual fluctuations and interindividual variability in copeptin concentrations, the mean CSF copeptin concentrations were obtained, and the general trend of copeptin before and after the day of vasospasm was assessed (Fig. 2B). Copeptin concentrations were significantly elevated prior to the day of onset of DIND, peaking 1 day after and subsequently decreasing. Data analysis of individual patients with a well-defined temporal pattern of copeptin matched this general trend of CSF copeptin increasing prior to the occurrence of DIND and then falling. However, a clear sequence of cause and effect between AVP and DIND cannot be concluded since this was a retrospective study.

Furthermore, therapy intensity may have interfered with copeptin levels and hence AVP levels, since both hypervolemia and the use of hypertonic saline could lead to an iatrogenic change in osmolality, which would in turn affect AVP release.²⁷

AVP may be used as a supplementary vasopressor in triple-H therapy that is refractory to standard catecholamine treatment.²² The administration of exogenous AVP could result in a reduction in endogenous AVP levels.

However, based on the retrospective review of patient records, none of our patients had received an AVP infusion or desmopressin on the days CSF was tested. There-

FIG. 4. Proposed interrelationships among AVP release, SIADH, hyponatremia, and cerebral ischemia. Dilutional hyponatremia from excess vasopressin release contributes to cell swelling, which exacerbates arteriole constriction by a direct pressure effect and contributes to cerebral ischemia. Excess vasopressin release may also cause increased arteriole constriction directly, thereby exacerbating cerebral ischemia. Alternatively, cerebral ischemia stimulates excess vasopressin release so that the resulting hyponatremia from SIADH is in fact an epiphenomenon of the underlying ischemia.

fore, the administration of exogenous AVP was not a potential confounding factor in our study. Although we could not establish that AVP causes DIND, our data indicate an association between increased AVP and DIND.

The Relationship Between Hyponatremia and DIND

An association between hyponatremia and DIND has been demonstrated in previous studies.^{7,21,27,30} While increased CSF copeptin alone is not predictive of DIND, a combination of increased CSF copeptin concentration and serum hyponatremia separates DIND patients from no-DIND patients (Fig. 3). However, the occurrence of DIND is not strictly associated with an absolute sodium value of < 135 mmol/L combined with elevated copeptin. A decrease in sodium value coupled with an increase in copeptin is also associated with DIND (Fig. 2A and B). This suggests that the simultaneous changes in copeptin and sodium values may be just as important as absolute values in relation to DIND.

Our results suggest that increased AVP is likely to be the unifying factor explaining the co-occurrence of hyponatremia and vasospasm-related DIND. Increased AVP is hypothesized to cause vasoconstriction via action on V_1

receptors. The simultaneous occurrence of falling or low serum sodium values is speculated to be due to the concurrent, excessive action of AVP on renal V_2 receptors, which causes water to be retained, leading to dilutional hyponatremia. Based on these hypotheses, the use of a mixed V_1/V_2 AVP receptor antagonist specifically in patients who develop SIADH after aSAH could potentially have the dual advantage of reducing cerebral vasoconstriction and water retention. An alternative explanation is that microvessel ischemia in the context of DIND results in excessive AVP release by the posterior pituitary, leading to SIADH (Fig. 4).

Limitations

This study involved the retrospective review of patient data, and therefore there was the potential for selection bias. Furthermore, it was not possible to establish cause and effect with regard to the relationship between increased copeptin levels and DIND.

Conclusions

Our findings indicate that a hyponatremic state combined with elevated or increasing CSF copeptin concentrations is associated with DIND. Increased AVP may be the unifying factor explaining the co-occurrence of hyponatremia and vasospasm-related DIND. However, because our study was small and involved a retrospective review of patient data, we cannot conclusively state that there is a cause and effect relationship between AVP elevation and DIND. Future studies are indicated to investigate the potential of an AVP antagonist to reduce the occurrence of DIND in patients who develop SIADH after aSAH.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Adamides, Fernandez, Barakat, Ziogas. Acquisition of data: Adamides, Fernandez, Barakat, Ziogas, Frugier, Stylli. Analysis and interpretation of data: Adamides, Fernandez, Barakat, Ziogas, Frugier, Laidlaw, Kaye. Drafting the article: Adamides. Critically revising the article: all authors. Reviewed submitted version of manuscript: Adamides. Approved the final version of the manuscript on behalf of all authors: Adamides. Study supervision: Adamides.

Supplemental Information

Previous Presentations

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