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Noninvasive monitoring in a patient with SAH diagnosis treated with Cerebrolysin – case report and review of the literature

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Abstract. – BACKGROUND: Subarachnoid hemorrhage (SAH) causes a high percentage of deaths and rehabilitation failures. Despite endovascular and surgery treatment algorithms, there is still no consensus on the guidelines for monitoring and neuroprotective treatment of patients.

CASE REPORT: We report a case of a patient with SAH treated endovascularly. The patient was hospitalized in the intensive care unit and monitored using Near Infrared Spectroscopy (NIRS) and Optic Nerve Diameters Assessment (ONDS).

CONCLUSIONS: Early and high-dose Cerebrolysin was used safely as neuroprotective treatment intravenously. The treatment using Cerebrolysin and additional monitoring was beneficial for the patient.

Key Words:
Noninvasive monitoring, SAH, Neuroproptective treatment, NIRS, ONDS.

Introduction

Subarachnoid hemorrhage (SAH) remains one of the most common causes of death and failure to return to social life. It results from both damage to the nervous system and indirect systemic complications[1]. The harmful effects of the first stage of aneurysm rupture include increased intracranial pressure (ICP), hydrocephalus, the risk of re-bleeding, and other complications such as vasospasm, delayed cerebral ischemia (DCI), seizures, hyponatremia, myocardial injury or arrhythmias, and pulmonary edema[2]. The frequency of SAH decreases (depending on trends, e.g., smoking), or remains at the same level depending on the data origin[3-5]. The risk factors include smoking, hypertension, heavy alcohol consumption, cocaine, hypercholesterolemia, diabetes mellitus, female sex[6,7]. Non-traumatic Aneurysmatic Subarachnoid Hemorrhage (aSAH) occurs with a frequency of 2-10% of all stroke events depending on the population[4]. The most common site of aneurysm formation in the central nervous system (CNS) is the anterior communicating artery (30.1%), posterior communicating artery (28.7%), and middle cerebral artery (15.9%)[4]. The prognosis of patients is affected, among others, by neurological status on admission, patient age, and volume of the damaged brain tissue[8]. The regional treatment differences compared in North America, Africa, Europe, and Australia did not affect the outcome of SAH treatment[8]. Basic neurosurgical and neuroradiological recommendations concerning treatment guidelines of SAH are available. However, there is still no consensus on neuroprotective treatment and monitoring methods for patients with diagnosed SAH.

Near Infrared Spectroscopy (NIRS) is a non-invasive monitoring method that has been shown[9] to be useful in assessing patients and autoregulation of cerebral circulation after SAH. It is also compatible with fluctuations in the Glasgow Coma Scale (GCS), as proven by Healy et al[10]. NIRS uses the near-infrared spectrum of light to reach the brain tissue and determines the ratio of oxygenated to deoxygenated hemoglobin, state of cytochrome c oxidase oxidation, and regional saturation oxygenation (rSO_2). With the

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use of two electrodes placed in the frontal area, a continuous measurement of the oxygenation of brain tissues from mainly venous vessels can be obtained. Evaluations can only be made as trends characteristic for a given patient, however, it is assumed[2] that the desaturation includes values for rSO_2 below 50%, or a reduction by 20% of the measurements. It is an easy-to-use, inexpensive method and does not require extensive personnel training. Although the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care (NCS MM)[11] recommended the use of NIRS in 2014 only for research purposes, later reports[2] increasingly proved that it can be used in traumatic brain injury (TBI) and SAH as extended monitoring as well.

Another non-invasive method remains Optic Nerve Diameters Assessment (ONDS). Ultrasound is a noninvasive, simple, bedside tool. It is widely used in the emergency room, as well as in the ICU[12]. Compared with Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), ultrasound has a low cost, high availability and does not require patient transport[2,12,13]. Studies[14,15] have proven the correlation between ONDS measurements on ultrasound with ICP invasively measured. The cutoff value for normal ICP measured with ONDS is 4.8 to 6 mm[14]. Most studies[14,15] find good specificity and sensitivity, showing high accuracy. Although ONDS could not be replaced for invasive ICP methods it has good sensitivity in recognizing increased ICP and could be very helpful in ICU, especially when it can be provided in systematic measurement points in everyday care[14,15].

Below we present a case of a patient with SAH treated by aneurysm coiling and then monitored in the ICU using NIRS and ONDS. During the hospitalization, extensive, early (within 6 hours after onset of symptoms (50 ml i.v.), high-dose neuroprotective treatment with Cerebrolysin was administered. Patients with SAH cannot be treated with a wide range of evidence-based neuroprotective drug options[16]. Cerebrolysin is an intravenously administered preparation of neuropeptides and free amino acids derived from porcine brain tissue. Its neuroprotective properties were clinically proven in patients with traumatic brain injury and stroke, mainly because of its anti-apoptotic and anti-inflammatory effects. The agent also reduces free oxygen radical concentrations and has neuroinflammatory response reductive properties[16].

Case Presentation

A 42-year-old Caucasian female was admitted to the hospital with a history of severe headache, left hemiparesis, and unconsciousness while traveling by car to work. The patient's history was not affected by modifiable risk factors: smoking, alcohol consumption, drugs, hypercholesterolemia, or diabetes mellitus. The angio-CT revealed a 5 mm ruptured anterior communicating artery (ACOM) aneurysm. Extensive bleeding into the subarachnoid space, with the largest amount of blood in the subarachnoid space surrounding ACOM artery complex, also in the lateral, III, and IV ventricles, was revealed. The visible widening of the temporal horns of the lateral ventricles indicated the beginning of hydrocephalus due to SAH (Figures 1 and 2). The patient was reported as Fisher grade IV and Hunt Hess grade IV, qualified for the coiling of the aneurysm (Figures 3 and 4).

After embolization, the patient was admitted to the ICU, and standard treatment was provided (mechanical ventilation, catecholamines in order to maintain mean arterial pressure (MAP), fluid therapy, and nutrition) with NIRS and ONDS monitoring (Table I and Figures 5 and 6). The pulmonary and cardiac functions were additionally monitored. The invasive blood pressure (IBP), heart rate (HR), and saturation (SO_2) were evaluated continuously. Because of the severe bleeding and patients' status at the admission, additional cardiac and pulmonary parameters were obtained using calibrated transpulmonary thermodilution method. Thermodilution allowed us to monitor not only cardiac index (CI), stroke

Figure 1. Noncontrast brain computed tomography shows subarachnoid hemorrhage, Fisher IV grade.

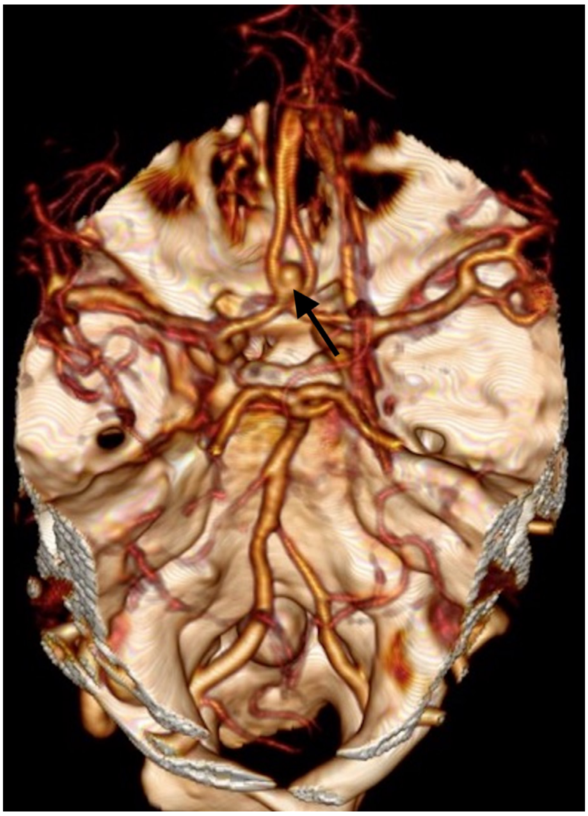

Figure 2. 3D reconstruction of a rotational angiography demonstrates the 5 mm aneurysm of the anterior communicating artery.

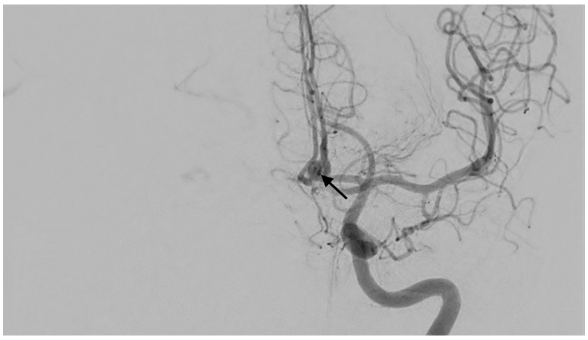

Figure 3. Digital subtraction angiography (DSA) shows the aneurysm of the anterior communicating artery.

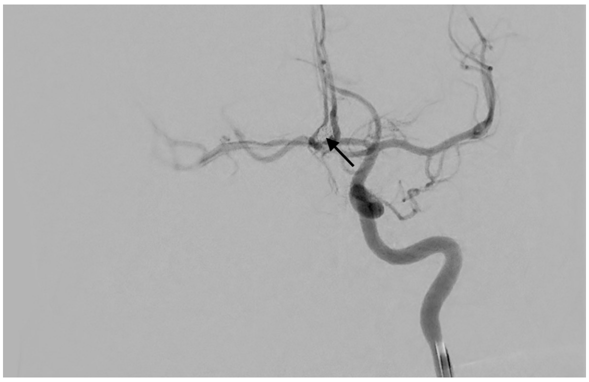

Figure 4. Post-procedural digital subtraction angiography (DSA) shows dense packing by platinum coils and total occlusion of the aneurysm.

volume index (SVI), and systemic vascular resistance index (SVRI) but also elevated extravascular lung water index (ELWI) to provide the most accurate hemodynamic and ventilation conditions.

Within the first 6 hours after the admission to the hospital, Cerebrolysin in a dosage of 50 ml per day was administrated intravenously. The administration continued for 14 days. At the admission to the ICU, the patient was unconscious, artificially ventilated, with symmetrical corneal- and cough reflexes, with the symmetrical and normal reaction of both pupils. For pharmacological sedation, fentanyl, propofol, and midazolam were administrated.

During the hospitalization, intravenous Cerebrolysin was continued for 14 days. No adverse effects of the drug were observed. The patient was rehabilitated already in the first week after the endovascular procedure. Initially, the rehabilitation was passive, during the pharmacological coma, then active after regaining consciousness.

Figure 7 below shows the patient's history from the symptoms' onset to the transfer to the rehabilitation department.

Table I presents ONDS and NIRS parameters during the ICU stay.

Figures 5 and 6 present the graphical representation of the ONDS and NIRS results.

Table I. ONDS and NIRS parameters during the ICU hospitalization.

Day of hospitalization	1	2	3	4	5
ONDS [mm]	L0.7 P0.6	L0.7 P0.6	L0.7 P0.6	L0.6 P0.6	L0.6 P0.6
NIRS [%]	P73 L69	P68 L70	P70 L66	P 70 L66	P61 L62

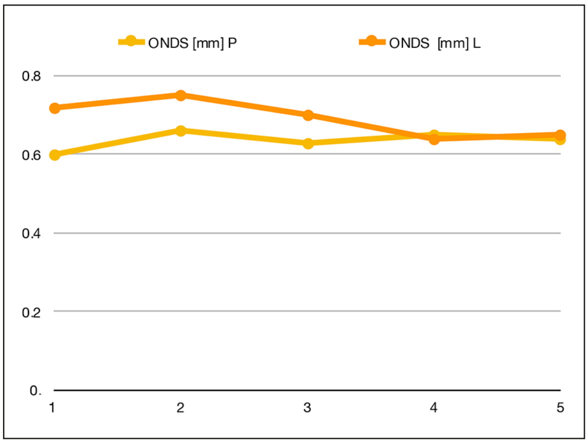

Figure 5. ONDS parameters during first 5 days of ICU hospitalization.

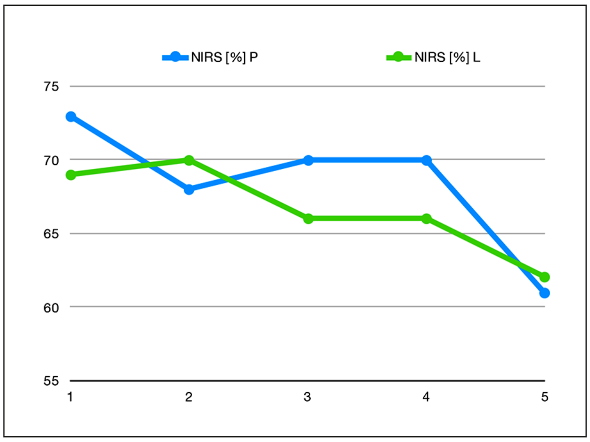

Figure 6. NIRS parameters during the first 5 days of ICU hospitalization.

Logical contact with the patient was observed from day 7. The patient was extubated on day. In the first period after extubation, patient's communication was limited to head movements. Significant paresis of the left upper limb and weakened movement in the lower limbs were also observed. Those symptoms gradually resolved during further treatment and rehabilitation. In the following days, the patient was conscious with a GCS of 14 (E4V4M6). In the neurological assessment, global weakening of muscle strength 1/5 m, and motor asymmetry P>L were noticed. Coughing and swallowing reflexes were normal. After 26 days of hospitalization, the patient was transferred to the rehabilitation ward.

Discussion

Available management standards for patients with SAH cover the basics of neurosurgical, neuroradiological, and intensive care procedures in severe patients. However, there is no consensus on monitoring and neuroprotective treatment.

Standards of care include the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach to assess and treat the patient as soon as possible, as delays are associated with poor outcomes. The management of patients includes the widely understood physiology: PaO_2, $PaCO_2$, PH, CO, Hb, Ht, glucose, Na, and normal coagulation. The recommended monitoring includes CT, and ICP - so far always considered the gold standard, despite possible complications. However, in the ICU, non-invasive methods are being used with increasing frequency. Many researchers[11,17,18] agree that monitoring should be multimodal and focused on the individualization of treatment and observation of the patient.

Invasive monitoring methods achieve the accuracy of the examination by being in the center

Home

Car driving - first symptoms-

Severe headache
Left hemiparesis
Unconsciousness

Ambulance

Emergency room

Intubation
Cerebrolysin i.v.

Neuroradiology - endovascular treatment

Intensive care unit
Treatment
Cerebrolysin continuation
Monitoring -NIRS, ONDS
Rehabilitation

Rehabilitation ward

Figure 7. Patient's history from the onset of the symptoms to the rehabilitation ward.

of the pathology: invasive ICP, brain temperature, brain oxygen tension, neurochemistry with the use of microdialysis, cerebral blood flow, and jugular oxygen saturation have the advantage of being close to the injured area. However, several disadvantages, such as high expenses, risk of complications, and the need for intensive personnel training, are involved as well. In recent years, monitoring has been shifting towards non-invasive methods which are easy to use, quickly available and allow patient observation in a continuous mode. Those methods are, i.e., NIRS, ONDS, Electroencephalography (EEG), Transcranial Doppler Ultrasound (TCD). The main advantages of these approaches are safety of use, ease, portability and usually lower costs[2].

More than 10 years ago, the first reports[19] on the correlation of NIRS with Cerebral Blood Flow (CBF) based on CT perfusion in patients with SAH were published. The authors confirm the good correlation between NIRS and TCD in patients after embolization (the trial included over 50 patients). The literature emphasizes the need for more studies to standardize the measurements and determine the cut-off points[20]. It has been found[21] that NIRS reliably and continuously assesses cerebral autoregulation in patients diagnosed with SAH and predicts information on vasospasm. NIRS could be as effective as TCD and may replace it in the future. NIRS is also more convenient and requires less attention and training[22]. In the pathophysiology of SAH, in addition to vasospasm, ischemia, microthrombosis, and impaired autoregulation occur early after trauma. It is, therefore, extremely important to be aware of delayed ischemic neurological deficits. NIRS changes in waves can precede an impending ischemic episode[22]. With monitoring of MAP, ICP, T, and oximetry, patients can nowadays receive a therapy focused on individual cerebral autoregulation[23-25].

So far, there are no clear reports on the correlation of one non-invasive monitoring method with others, and from reports with few patients, it is difficult to generalize results. One of the reports describes the NIRS/ONDS correlation in children with suspected high ICP. The ONDS corresponded with an increase in ICP, however, the correction between NIRS and ONDS was not shown[24]. Due to its advantages, NIRS is an increasingly widespread method in monitoring patients with SAH, although there are still no prospective large studies assessing its effectiveness[26].

In our case, despite the laterality of the damage (as it results in the majority of SAH cases), bilateral electrodes in accordance with the producer's recommendation were used. As shown in Figures 5 and 6, the fluctuations on NIRS measurements corresponded with the ONDS changes.

Considering previous safety reports[16] on the use of Cerebrolysin in SAH patients, we decided to use the agent in a 50 ml daily dose and within a 6-hour period after the onset of the first symptoms. We did not observe any side effects after the administration of Cerebrolysin. Despite the unfavorable prognosis of high blood glucose levels on admission and severe radiologic and clinical features (Hunt Hess - IV, Fisher IV grade), the condition of the patient after treatment was relatively good (GCS15)[27].

The evidence from retrospective studies[20] concludes that SAH mortality was reduced in the Cerebrolysin groups. However, no randomized studies are available on that matter.

According to Woo et al[16], Cerebrolysin was proven to have no complication in patients with SAH (n=50 receiving the drug *vs.* placebo), and in our case, the treatment also was not associated with side effects.

Conclusions

The early administration of 50 ml Cerebrolysin daily dosage was safe in the presented case. The overall effect of the treatment was good. In conclusion, after analyzing the literature and based on the positive experience with our case, it seems reasonable to consider combining different non-invasive monitoring with extended neuroprotective treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

K. Kojder and K. Jarosz: editing, final revision, final approval; K. Kojder, J. Solek-Pastuszka and K. Kubiak: writing, final revision, final approval; W. Poncyljusz and A. Andrzejewska, writing, final revision, final ap-proval. All authors read and approved the final version of the manuscript.

Informed Consent

The patient gave her consent to the publication. IRB approval was waived.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Pomeranian Medical University Bioetical Committee, Szczecin, Poland - No. KB-0012/88/16.

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