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Case Report
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# Hair Cortisol as a Biomarker of Stress before and after Subarachnoid Hemorrhage: A Case Report

*Sörbo A[1,2]*, Eiving I[3], Theodorsson E[4] and Rydenhag B[5]*

[1]Department of Neuro-and Rehabilitation, Southern Älvsborg Hospital, Borås, Sweden

[2]Department of Neuro- and Rehabilitation, Uddevalla Hospital, NU Hospital Group, Uddevalla, Sweden

[3]Department of Anesthesiology and Intensive Care, Sahlgrenska University Hospital, Göteborg, Sweden

[4]Department of Clinical Chemistry and Experimental Medicine, Linköping University, Linköping, Sweden

[5]Department of Clinical Neuroscience and Rehabilitation, University of Gothenburg, Göteborg, Sweden

## Abstract

The aim was to study stress in the acute and post-acute phase in patients with severe traumatic brain injury (TBI) or non-traumatic subarachnoid hemorrhage (SAH) who were treated at the neurointensive care unit (NICU). Hair cortisol is a biomarker of stress via alterations in hypothalamus-pituitary-adrenal axis activity, where cortisol from plasma is continuously incorporated into growing hairs at their roots. As hair grows at an average of 1 cm/month, concentrations of hair cortisol can also be used to measure stress levels retrospectively.

Hair samples were collected at an interval of one month until three months, with the first cut at admission to the NICU. The patients (or their relatives, if the patient was unable to communicate) were interviewed about psychological or physical stressors during the previous months.

We present a 28-year-old woman suffering from a subarachnoid hemorrhage (SAH), studied with repeated haircuts. She experienced the sudden onset of a severe headache. The general practitioners diagnosed it as migraine or wry neck. Three weeks later, she experienced another attack of severe headache. A CT scan showed an SAH. Six months after the SAH, the patient developed hydrocephalus and was successfully treated with a VP shunt. In this case, hair cortisol was elevated during the pre-hospital month (probably because of pain and stress due to a sentinel or "warning" leak), during the intensive care period and until two months after the SAH. It then normalized, but it was elevated again at the time at which the patient developed hydrocephalus. At the nine-month haircut, her hair cortisol had again normalized.

This case indicates that hair cortisol measurement is a promising method for studying stress, retrospectively and during recovery, in patients suffering from SAH.

**Keywords: Traumatic brain injury; Subarachnoid hemorrhage; Hair cortisol**

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***Correspondence:***
*Ann Sörbo, Department of Neuro- and Rehabilitation, Southern Älvsborg Hospital, SE-501 82 Borås, Sweden, Tel: +46(0)336164875; E-mail: ann.km.sorbo@vgregion.se*

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## Introduction

Exposure to stress is associated with the activation of the hypothalamic-pituitary-adrenal (HPA) axis which regulates the release of the glucocorticoid hormone, cortisol, from the adrenal cortex [1]. High levels of stress hormones and catecholamine are associated with subarachnoid hemorrhage (SAH) [2-3]. Cortisol excretion in blood and saliva after severe traumatic brain injury (TBI) and SAH has previously been studied [4-7]. Measuring cortisol in saliva, plasma or urine, however, reflects cortisol concentrations at the time of collection and not long-term exposure to stress. Repeated collections during 24 h are needed, as cortisol is released with a so-called circadian rhythm, at least in healthy humans [1,4]. The circadian rhythm has been found to be disturbed in analgo-sedated intensive care unit patients [4].

Assessments of hair cortisol may reflect long-term change and have attracted increasing interest as a biological marker of stress in different diseases [8-12]. Hair grows at an average of 1 cm/month and offers a unique opportunity to measure stress levels retrospectively as well [12,13].

In spite of this, little is known about long-term cortisol in patients before and after severe brain injury. We therefore became interested in studying hair cortisol as a biomarker of stress in the acute and post-acute phase in patients who were treated at the neurointensive care unit (NICU).

In this case report, we present one of the interesting cases from our study, a woman suffering from SAH.

## Materials and Methods

This study was approved by the Regional Ethical Review Board at the University of Gothenburg and informed consent was obtained from the participants.

In this paper, we present an interesting case, a 28-year-old woman suffering from SAH. Hair samples were collected on admission to hospital, monthly until three months and at six months, nine months and 3½ years after the SAH.

Hair samples were cut from the posterior vertex close to the scalp. Cortisol was measured from the one-cm hair segment near the scalp. The cortisol analysis was performed using a competitive radioimmunoassay in methanol extracts of hair samples frozen in liquid nitrogen and mechanically pulverized. This method is described in the work presented by Karlén et al. [13].

The patient was interviewed by a research nurse using open questions. She was asked about her medical history and psychological stressors, such as serious life events, during the last three months before the SAH and the same questions were asked about the previous month at each subsequent assessment.

The medical records from the general practitioner (GP), the NICU, the neurosurgery department and the rehabilitation clinic were analyzed retrospectively.

## Results and Discussion

This 28-year-old woman had previously been healthy, except for mild depressive symptoms, which had been well treated with antidepressants.

She woke up one morning with a severe headache and neck pain. Just before the onset of the headache, she had separated from her boyfriend. Two days later, she went to her GP, as the symptoms had not declined. The GP noted that she was "tender" bilaterally in the neck muscles, had nausea and was photophobic. The diagnoses were suspected migraine and a wry neck and the GP prescribed sumatriptan.

Five days later, she visited her GP again because of a worsening headache and neck pain when taking sumatriptan. She was assessed by another GP who noted that she had no focal neurology signs and was "unaffected" but was sitting with a "straight and fixed back". The neck muscles were stiff bilaterally, but she was able to bend her chin to her breast. The GP queried the previous diagnosis and suspected there was an inflammation in the muscles of the neck. The patient was then prescribed an NSAID.

The pain persisted and, three weeks later, the patient experienced another attack of an even more severe headache, dizziness and nausea. She was referred to hospital with nausea, dizziness, severe headache and nuchal rigidity, but she was awake, with no focal neurology corresponding to Glasgow Coma Scale 15 [14], WFNS grade 1 [15] and Hunt & Hessgrade 2 [16]. A spontaneous SAH was diagnosed by a CT scan (Fisher grade 4) [17] and a cerebral angiography revealed a saccular aneurysm in the right distal vertebral artery. It was successfully treated by endovascular embolization on the date of hospital arrival. The patient was mechanically ventilated during embolization and for a short period during surgery to enable the insertion of an external ventricular drainage (EVD) catheter, as, on the third day, she developed acute hydrocephalus. The intracranial pressure was monitored and the EVD remained in place for 13 days. On the sixth day, vasospasm was detected by Doppler ultrasonography and she was prescribed high-dose nimodipine treatment. Norepinephrine was given for seven days and dobutamine for three days because of low blood pressure. The patient was not treated with midozolam or beta-blockers. She had a headache which required pharmacological treatment with ketobemidone and paracetamol, but she was awake and oriented (GCS 15) during her stay at the NICU.

The hospital stay was 23 days, with 12 days at the NICU and 11 days on the neurosurgery ward, followed by inpatient rehabilitation for 14 days and, after two months, outpatient rehabilitation for five weeks. During the outpatient rehabilitation period, she suffered from mental fatigue, slight paresis in her right hand with problems opening tins, balance problems, attention-deficit and concentration-deficit disorder. She was more sensitive to stimuli from her surroundings and sensitive to stress.

Six months after the SAH, the patient visited the emergency department because of an oppressive headache, dizziness and severe fatigue. The medical investigation, including a CT scan, revealed hydrocephalus. She was successfully treated with a ventriculo-peritoneal shunt. The patient was very worried and stressed before the operation.

One month after the shunt operation, the patient still reported mental fatigue and some dizziness now and then. She also noted some discomfort from her stomach, but she had recovered well. The shunt had to be adjusted a few times because of over-shunting.

She then recovered further, had no more problems with her hand and was able to lead an independent life. After nine months, she was on sick leave but was studying at a "people's high school" and was cohabiting with a new partner. At the 3½ year follow-up, she was still on sick leave, with an outcome corresponding to GOSE 6 (Glasgow Outcome Scale Extended) [18].

According to the hair cortisol level measurements, this patient's hair cortisol was elevated during the pre-hospital month (first haircut on arrival at the NICU), during the intensive care period and hospital stay (second haircut) and until two months after the SAH. It had normalized three months after the SAH (fourth haircut) but was elevated at the time at which the patient developed hydrocephalus (fifth haircut). At the nine-month haircut, it had normalized again, but, at the last haircut, there was an extremely elevated value, see (Table 1).

This patient had elevated hair cortisol levels before the verified SAH. The reason for the elevated cortisol concentrations before the bleed could be that she had had a severe headache for three weeks because of a suspected sentinel or "warning" bleed and, in addition, she had recently separated from her boyfriend and also had a minor depression.

There was an HPA response during the four weeks after the SAH, corresponding to the time of the treatment at the NICU and

**Table 1:** Hair cortisol (pg/mg).

| At the NICU | 1 month | 2 months | 3 months | 7 months HP, VP shunt | 9 months | 3½ years |
|---|---|---|---|---|---|---|
| 108.9 | 386.2 | 140.1 | 15.6 | 70.0 | 26.7 | 12014.3 |

(Normal value 16-84 pg/mg)
NICU: Neurointensive Care Unit; HP: Hydrocephalus; VP: Ventriculoperitoneal

emergency ward, with an increase in hair cortisol. Intensive care treatment, as well as the brain injury itself, is known to cause stress [2,3,7,19]. The pharmacological treatment during her stay at the NICU could be suspected of having an impact on her cortisol levels [7,20]. In this case, however, we suggest that none of the administered drugs is able to explain the results.

The patient reported significant stress at the time of developing hydrocephalus and treatment (shunt operation). This once again produced elevated hair cortisol, thereby supporting the hypothesis that this method could be of value for measuring chronic stress in these patients.

A satisfactory response by the HPA axis is important for survival and recovery after a severe disease [19,21].

As there was an extreme value at the last haircut, the patient was again asked about her medication. She reported that, at this time, she had used a cream containing betamethasone (a corticosteroid) because of eczema. We thus suggest that the last sample was contaminated.

Long-term cortisol measurements are not suitable for short-term measurements in the acute phase at the NICU, but they could be a complement in the investigation of patients who suffer from severe fatigue after a brain injury/bleed or for following stress reactions during rehabilitation in the long term.

Deficient cortisol secretion following severe injury has been described by Cernak et al. [21] among others. Severe brain injury may increase the risk of developing acute and chronic hypopituitarism. Pituitary hormone alterations that develop in the early recovery phase and during rehabilitation after brain injury may have implications for long-term functional recovery [22].

In previous studies, hair cortisol has been found to correlate strongly with blood and salivary cortisol and is a promising method for identifying hypopituitarism as a complement to early morning plasma cortisol levels and for long-range assessments of chronic stress, both retrospectively and during recovery after brain injury. Possible applications include identifying the patients who are in need of pharmacological substitution with cortisone because of hypopituitarism (low levels), or will require stress-reduction therapy because of persistent chronic stress reactions after the SAH (chronically elevated hair cortisol levels).

## Conclusion

To summarize, this case illustrates that stressful events before and after the SAH produced elevated hair cortisol and non-stressful periods resulted in normalized hair cortisol levels, which implies that this patient experienced a satisfactory response from her HPA axis.

This study suggests that hair cortisol measurement is a promising method for long-range assessments of stress, both retrospectively and during recovery after SAH. It is important to be aware of the possibility of biased results because of contamination.

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