Dynamics of selected biomarkers in cerebrospinal fluid during complex endovascular aortic repair - a pilot study: Spinal fluid biomarkers in aortic repair

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Abstract:

Introduction: Ischemic spinal cord injury (SCI) is a serious complication of complex aortic repair. Prophylactic cerebrospinal fluid (CSF) drainage, used to decrease lumbar cerebrospinal fluid (CSF) pressure, enables monitoring of CSF biomarkers that may aid in detecting impending SCI. We hypothesized that biomarkers, previously evaluated in traumatic SCI and brain injury, would be altered in CSF over time following complex endovascular aortic repair (cEVAR).

Objectives: To examine if a chosen cohort of CSF biomarker correlates to SCI and warrants further research.

Methods: A prospective observational study on patients undergoing cEVAR with extensive aortic coverage. Vital parameters and CSF samples were collected on ten occasions during 72 hours post-surgery. A panel of ten biomarkers were analyzed (Neurofilament Light Polypeptide (NFL), Tau, Glial Fibrillary Acidic Protein (GFAP), Soluble Amyloid Precursos Protein (APP) α and β, Amyloid β 38, 40 and 42 (Aβ38, 40 and 42), Chitinase-3-like protein 1 (CHI3LI or YKL-40), Heart-type fatty acid binding protein (H-FABP).).

Results: Nine patients (mean age 69, 7 males) were included. Median total aortic coverage was 68% [33, 98]. One patient died during the 30-day post-operative period. After an initial stable phase for the first few postoperative hours, most biomarkers showed an upward trend compared with baseline in all patients with >50% increase in value for NFL in 5/9 patients, in 7/9 patients for Tau and in 5/9 patients for GFAP. One patient developed spinal cord and supratentorial brain ischemia, confirmed with MRI. In this case, NF-L, GFAP and tau were markedly elevated compared with non-SCI patients (maximum increase compared with baseline in the SCI patient versus mean value of the maximal increase for all other patients: NF-L 367% vs 79%%, GFAP 95608% versus 3433%, tau 1020% vs 192%).

Conclusion: This study suggests an increase in all ten studied CSF biomarkers after coverage of spinal arteries during endovascular aortic repair. However, the pilot study was not able to establish a specific correlation between spinal fluid biomarker elevation and clinical symptoms of SCI due to small sample size and event rate.

Introduction

A highly dreaded complication related to complex aortic repair of thoracic or thoracoabdominal aneurysms (TAA) is ischemic spinal cord injury (SCI), with incidence ranging from 2 up to 31% [1–13] depending on the type of reconstruction. The risk for this complication has not improved in recent years, despite advances in aortic surgery with endovascular techniques. In contrast to traditional open TAA repair, when intercostal arteries can be re-implanted to the aortic graft to reduce the risk for SCI, endovascular repair often entails extensive coverage of the aorta and its intercostal and lumbar arteries without revascularization. Spinal ischemia in these procedures occurs due to impaired blood flow to the spine with exclusion of tributaries from intercostal arteries (including the artery of Adamkiewicz), lumbar- and sacral arteries, and sometimes also hypogastric and subclavian arteries [8,14]. The symptoms from spinal ischemia vary from sensory lower limb deficits, urine and fecal incontinence to paraplegia [9].

Measures to reduce the risk for SCI during endovascular complex aortic repair are based on maintaining optimal spinal cord perfusion by increased mean arterial pressure and decreased lumbar cerebrospinal fluid (CSF) pressure using a spinal drainage [8,9,15,16]. Both of these measures may have potential dangerous side effects. In addition, detection of SCI during and early after the operation is difficult due to the sedation used perioperatively.

A rapidly evolving research area is the search for a “troponin” of the central nervous system. In SCI, a specific biomarker would be of great value as it could help indicating risk for serious neurologic deficits in anaesthetized patients, or indicate early signs of SCI prior to clinical symptoms to enable measures to prevent established permanent ischemic damage. The ideal SCI biomarker should, alongside being specific for the central nervous system, have rapid and significant release into the blood. It should preferably also be eliminated within a few hours, easily analyzed and predict the seriousness of the injury [17].

Elevation of certain biomarkers after traumatic spinal cord injury and during neurodegenerative diseases is a fairly well described [18]. However despite previous efforts, no established biomarkers exist for SCI after aortic surgery[19]

The current pilot study aimed to assess the feasibility and potential use of elective cEVAR as an experimental-like model for studies of spinal ischemia and to explore a high number of selected biomarkers in CSF to detect SCI. We hypothesize that extensive aortic coverage with an endovascular stent-graft results in an instantaneous SCI hit, regardless of

whether the patient develops symptoms or not. In this study, patients received a prophylactic spinal drain prior to and until 72 hours after repair as part of the routine measures to prevent SCI after cEVAR. This resulted in a possibility to assess the dynamics of the selected biomarkers in CSF before and after coverage of several intercostal arteries during hemodynamic control. Ten different biomarkers were analyzed for up to three days after aortic coverage.

Materials and methods

Biomarkers

A review of the spinal fluid biomarkers with their respective attributes, relation to central nervous system damage and methods of analysis is given in table 1.

Table 1

Biomarker	Description	Relation to neuro-pathology	Method for analysis
Neurofilament Light Polypeptide (NFL)	Intermediate filament protein specific to neurons. Contributes to axonal transport and structural support[20]. A marker of axonal injury	Increased levels in patients with SCI after aortic repair[21,22] with possible correlation between magnitude of the biomarker to severity of disease[23,24].	Commercially available ELISA (NF-Light, Uman Diagnostics, Umeå, Sweden).
Tau	Found in abundance in neurons, contribute to axonal transport[20]. A marker of axonal injury	Increased levels in patients with SCI after aortic repair[21] with correlation between magnitude of the biomarker to severity of traumatic spinal cord injury[25].	Commercially available ELISA (INNOTEST® hTAU Ag, Fujirebio, Ghent, Belgium)
Glial Fibrillary Acidic Protein (GFAP)	Intermediate filament protein, primary found in astrocytes[26]. A marker of astrocytic activation	Increased levels in SCI after aortic repair[22,27,28] and correlations between magnitude of the biomarker to severity of traumatic spinal injury[20,25].	In house ELISA (ref: Rosengren LE, Wikkelso C, Hagberg L. A sensitive ELISA for glial fibrillary acidic protein: application in CSF of adults. J Neurosci Methods 1994;51:197–204).
Soluble Amyloid Precursor Protein (APP) α and β	Integral membrane protein, abundant in synapses of neurons[29]. A marker of non-amyloidogenic APP processing, and β, a marker of amyloidogenic APP processing.	Mostly studied in regard to neurodegenerative disease. Elevated in reversible ischemia[30].	Commercially available immunoassay with electrochemiluminescence detection (sAPP Duplex kit, Meso Scale Discovery, Rockville, MD).
Amyloid β 38, 40 and 42 (Aβ 38, 40 and 42)	Markers of amyloidogenic APP processing, where Aβ 42 specifically related to Alzheimer-associated plaque pathology	Decreased in Alzheimer´s disease due to assembly into Aβ aggregates. Decreased levels may	Commercially available immunoassay with electrochemiluminescence detection (Abeta Triplex kit,

		indicated reduced synaptic transmission [30].	Meso Scale Discovery, Rockville, MD)
Chitinase-3-like protein 1 (CHI3LI or YKL-40)	Glycoprotein found in various cells of the body. Associated with tissue remodeling, inflammation and fibrosis[31]. A marker of astrocytic activation.	A role in neurodegeneration is suggested [32].	Commercially available ELISA (R&D Systems, Minneapolis, MN).
Heart-type fatty acid binding protein (H-FABP)	Cytoplasmic protein mostly known due to being released from cardiac myocytes during ischemia[33]. Also a marker of neuronal injury.	A role in neurodegeneration and ischemia[32,34].	Commercially available immunoassay with electrochemiluminescence detection (MSD® Human FABP3 kit, Meso Scale Discovery, Rockville, MD).

Study design

A prospective observational pilot study was performed where clinical data and CSF samples were collected for patients undergoing endovascular aortic repair with insertion of prophylactic spinal drainage. The study was approved by the ethic committee and individual informed consent was acquired.

Patient demographic and operative data

Patients who underwent elective cEVAR with >20cm aortic stent-graft coverage due to aortic aneurysm (degenerative or post-dissection) and got prophylactic CSF drainage were consecutively included.

Clinical data were recorded including comorbidities (prior aortic surgery, chronic obstructive pulmonary disease, renal insufficiency, cardiovascular disease, hypertension), type of aneurysm, maximum diameter, type of operation (acute or elective), total aortic coverage, zones for proximal and distal stentgraft landing according to Fillinger et al. [35], coverage of subclavian or internal iliac artery, post-operative complications, length of stay in ICU and ward.

Patients who developed symptoms of SCI after surgery were treated with 1) elevation of blood pressure with aim of MAP>85mmHg, 2) blood transfusions with the aim of hemoglobin values >100g/L, 3) increased spinal fluid drainage up to 20ml/hour, and 4) oxygenation with aim of central venous oxygen saturation of >75%. Generally, patients were extubated after aortic repair prior to transfer from the operating room. If extubation was not possible, wake-

up test was performed prior to departure from the operating room to assess neurology, and four times daily thereafter.

Spinal fluid sample collection

Spinal drainage was inserted by attending anesthesiologist prior to surgery. The drainage volume was controlled with the use of the LiquoGuard system (LiquoGuard, Möller Medical GmbH, Fulda, Germany), with the standard setting of drainage of up to 10ml CSF/h at a CSF pressure of >10cmH2O when the patient was sedated, and 2ml CSF/h in awake asymptomatic patients. Repeated sampling was done up to ten times in the period during which the patient had the spinal drain in place. These CSF samples, 1-1.5ml each, were obtained at 1) at introduction of spinal drainage, 2) after induction of anesthesia (baseline sample), 3-10) 0-5 minutes, 15 minutes, 30 minutes, 1 hour, 3-6 hours, 20-28 hours, 44 – 52 hours and 72-80 hours after completion of aortic stent-graft coverage. Each CSF sample was frozen and kept at <70 ºC prior to analysis.

Biomarker analysis

Ten biomarkers (NF-L, tau, GFAp, sAPPα, sAPPβ, Aβ38, Aβ40, Aβ42, YKL-40, H-FABP) were measured using the methods described in Table 1. The measurements were performed in one round of experiments using one batch of reagents by board-certified laboratory technicians who were blinded to clinical data. The measurements were performed as singlicates and internal quality control samples run as duplicates were used to monitor analytical variation; intra-assay coefficients of variation were below 10% for all biomarkers.

Statistical analysis

Age, maximal aortic diameter and total aortic coverage is reported as median and range. Biomarker levels are reported as crude values, as well as rate of baseline value (sample value after induction of anaesthesia used as baseline). Missing samples were left out in graphs. Due to the exploratory nature of this study, no statistical analysis of sample values were performed.

Results

Patient demographics and clinical presentation

Nine patients were included in this pilot study, of whom one developed permanent spinal cord ischemia symptoms after operation. Clinical characteristics are presented in Table 2.

Peri- and postoperative data

Two patients were treated with thoracic endovascular aortic repair (TEVAR), two with branched repair (BEVAR), two with combined fenestrated and branched repair (F/BEVAR), and three with fenestrated repairs (FEVAR). Proximal and distal landing zones as well as perioperative data are presented in table 3.

Two patients underwent the operation in sub-acute settings due to symptomatic aortic aneurysm, one of which developed symptoms of SCI. This case is described in detail below. Two patients developed signs of stroke after the operation, diagnosed with computed tomography (CT). The first patient had multiple ischemic infarcts supratentorial bilaterally and a small hemorrhagic lesion in the right hemisphere. That patient also developed SCI. The other patient suffered a stroke two weeks post-operatively with new infratentorial bilateral ischemic lesions diagnosed on CT and magnetic resonance imaging (MRI) that was conservatively treated.

Three patients underwent re-operation < 30 days post-operatively. Two underwent laparotomy due to bleeding complications, of whom one also had bowel ischemia. In addition, one patient underwent an evacuation of femoral hematoma.

One patient developed a spinal drainage complication with subarachnoid bleeding at the lumbar level after removal of drain. His symptoms were paresis of the left leg in addition to sharp lower back pain. These symptoms were transient with later full recovery of the patient.

Spinal fluid biomarkers

The CSF biomarker outcome for the ten evaluated biomarkers is presented in Figure 1 A-J, and the crude values for all biomarkers are presented in Supplemental table 4-14. There was an important variation between patients in baseline values for all biomarkers. Therefore, for each individual, the biomarker level after induction of anesthesia was used as reference mark to assess individual changes in biomarker (increase or decrease versus the individual's baseline value over time in percentage), as presented in Figure 1 A-J. In the figures the one patient with symptoms of perioperative neurologic event (SCI as well as stroke) is represented with red color. Overall, after an initial stable phase for the first few hours, several of the biomarkers thereafter had an upward going trend compared to baseline. This increase compared to baseline typically occurred after stentgraft implantation and coverage of the

aortic side branches to the spinal cord, and was variable between patients, also among those without SCI symptoms, Figure 1 A-J. When we assessed the three patients with the highest increase in biomarker levels compared to baseline for each biomarker, we noted that two patients, in addition to the one who developed SCI, were amongst those who increased their biomarkers the most in eight different biomarkers. Another two had pronounced increases for six different biomarkers. However, we could not identify any pattern regarding pathology of disease, type of procedure or post-operative complications for those patients.

Patient with perioperative neurologic event

Postoperative spinal cord ischemia and stroke occurred in a 61 year old female (#5). She had history of hypertension, COPD and was a previous smoker without any prior aortic interventions. Indication for operation was a 66mm symptomatic Crawford's type 2 TAAA. She was operated on sub-acutely with carotid-carotid-subclavian bypass and BEVAR with revascularization of all visceral arteries. Aortic coverage was from zone one to nine according to the MALAN criteria, or 94%. Neither SCA nor IIA were occluded during the operation. The patient developed intraabdominal bleeding requiring reoperation with laparotomy on day one postoperatively. During this procedure, she required a short period of cardiopulmonary resuscitation due to cardiac arrest. Neurological symptoms were first noted on the second day post-operatively after reduction of sedation, with paraplegia and left unilateral arm paralysis. MRI showed multiple supratentorial ischemic lesions, as well as a spinal ischemic lesion at the level of the fourth thoracic vertebra, Figure 2. However, the spinal imaging was negatively affected by the presence of the metallic stentgraft in the adjacent aorta, creating artefacts. The patient died on post-operative day 45 due to multi-organ failure.

Eight samples were analyzed from the patient. These analyses showed a marked increase in biomarker concentrations of NF-L, GFAp and tau when compared to the other patients. The increase was most notable in the last samples taken 20-28 hours after induction of anesthesia. NF-L increased 467%, compared to 74-162% for the other patients. For tau, the corresponding increase was 1002% (compared to 100-454%) and for GFAP 95708% (compared to 110-2011%). H-FABP showed an increasing trend different from the other patients, exception being one patient (#9) who had significantly elevated H-FABP levels between samples 6 and 7 (3-6h-20-28h post-operatively); this specific patient suffered ischemic lesions in systemic organs (required laparotomy, bowel resection and bilateral thigh fasciotomies due to compartment syndrome).

An additional patient (#7) acquired stroke two weeks post-operatively with no visible upward trend of his biomarkers in comparison to other patients in the 72-hour post-operative period.

Discussion

The current report confirms the feasibility of CSF biomarker evaluation in complex endovascular aortic repair. Theoretically, extensive stent graft coverage of the aorta with subsequent redistribution of the spinal perfusion from intercostal arteries to collateral circulation results in hemodynamic changes in the spinal perfusion. This hemodynamic change may result in subclinical ischemia in some patients, and overt SCI symptom in others. Therefore, the evaluation of biomarkers in this setting mimics an experimental situation with varying degree of spinal ischemia depending on the collateral circulation of the specific patient. The use of a prophylactic spinal drain during complex endovascular aortic repair results in a possibility to evaluate biomarkers in CSF in conjunction with aortic stentgraft coverage. Among several neuro-biomarkers studied in this report, NFL, GFAP and TAU protein were identified as biomarkers with increased value in the patient with significant neuro-ischemic events. In addition to this, some patients without overt neurological deficits also showed increased biomarker levels after aortic coverage, potentially suggesting a role for biomarkers in assessing subclinical ischemia.

Despite significant developments in the field of endovascular aortic repair, the risk for ischemic SCI still persists in patients undergoing extensive aortic aneurysm repair. This is due to the change in hemodynamics and perfusion of the spinal cord. However, not all patients develop symptomatic SCI, and early identification of patients at risk for SCI is of great importance as this would offer a possibility for prophylactic measures to reverse or at least limit the injury. In this context, identification of a biomarker that would indicate presence of ischemia in the spinal cord would be of value. Additionally, a biomarker would facilitate the identification of SCI in patients who cannot be assessed clinically, e.g. due to delayed extubation after extensive aortic repair. Furthermore, identification of the biological pathways involved in development of SCI may offer further understanding regarding the therapeutic potential in treating SCI in early stages.

Although this report confirms that CSF biomarkers may be of value in evaluation of neuro-damage post aortic surgery, the study also unveils several challenges and limitations related to this experimental setting. Importantly, the complex aortic repair procedure may result in significant other clinical complications including ischemic lesions in

other organs, or development of supratentorial lesions, which may per se affect the biomarkers of interest. Additionally, the analysis of biomarkers indicates a significant difference in baseline value between individuals for several of these items. Therefore, definition of values which may be regarded as normal versus pathologic may be challenging. In the current analysis, the post-anesthesia baseline value was used for evaluation of changes in biomarker level on individual level.

We observed marked elevations of NFL, GFAP and tau in the patient who developed ischemic neurological lesions compared with the other patients. There was also a visible difference in the elevation of H-FABP between this patient and the others with the exclusion of one patient with ischemic complications in bowel and muscles. The patient with neurologic complication underwent cardiopulmonary resuscitation during the operation due to cardiac arrest which could also explain the elevation in H-FABP[33]. The onset of difference in the elevation of these three biomarkers was most noticeable in the sample taken 20-28 hours after the deployment of the stentgraft. The symptoms of SCI were first noted on post-operative day 2 which arises the question if prophylactic measurements could have been applied with earlier acknowledgement of neurologic lesions with the use of spinal fluid biomarkers. Early prophylactic measures could then arrange from increased spinal fluid drainage and elevation of mean arterial pressure to reintervention where blood flow to the aneurysmal sac could be restored. Study by Ullery et al. showed that majority of SCI develops in a delayed fashion with median occurrence at 10.6 hours post operatively[10].

Limitations of the current study include the small number of patients with only one incident of neurologic event during the time of spinal drainage, with combination of supratentorial and spinal cord lesions. While another patient developed cerebral lesions it was beyond the ability for comparison as the lesions appeared 2 weeks post-operatively and thus after the time period of spinal drainage. The sampling of spinal fluid for the evaluation of biomarkers also causes a limitation where CSF drainage has its own complications and the need for early removal often arises which can make patient comparison difficult.

The technique of using prophylactic spinal fluid drains as a protective measure against SCI has showed satisfying results after open repair in two randomized studies[36,37]. The use of spinal drainage in endovascular repair is however debated. Whilst many centers consider prophylactic CSF drainage to be indicated in cases with extensive aortic coverage, others argue that the risks and complications associated with the drains to outweigh its potential benefits[7,38,39]. Considering the risks that follow the usage of spinal drains the ideal CSF biomarker would be one who moves through the blood brain barrier, is measurable in

blood tests and elevates proportionally in serum to CSF. This would allow for much less invasive observation of biomarkers with regular blood tests and a selection based CSF drainage as a response to elevated blood biomarkers.

In conclusion, CSF biomarkers may prove useful in identification of early neurological events in patients undergoing extensive aortic repair. Further studies with extended number of patients are warranted to assess the possible role of NFL, GFAP and tau as biomarkers to predict and monitor ischemic SCI. Evaluation of biomarkers in blood in parallel with the CSF biomarker measurements would also be a valuable future study, supported by recent advancements in ultrasensitive measurement techniques and Single molecule array methods for plasma NF-L, GFAP and tau (ref: PMID: 32322100).

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Conflicts of interest

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

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