

Beta Trace Protein as a Potential Biomarker for CSF-Venous Fistulas

Ian T. Mark, Waleed Brinjikji, Jeremy Cutsforth-Gregory, Jared T. Verdoorn, John C. Benson, Ajay A. Madhavan, Jeff W. Meeusen

ABSTRACT

BACKGROUND AND PURPOSE: Accurately identifying patients with CSF-venous fistulas (CVF), one cause of spontaneous intracranial hypotension (SIH), is a diagnostic dilemma. This conundrum underscores the need for a CVF biomarker to help select who should undergo an invasive myelogram for further diagnostic workup. Beta trace protein (BTP) is the most abundant CNS derived protein in the CSF and therefore is a potential venous biomarker for CVF detection. The purpose of our study was to measure venous BTP levels as a potential CVF biomarker.

MATERIALS AND METHODS: We prospectively enrolled 14 patients with CVF and measured BTP in venous blood samples from the paraspinal veins near the CVF and compared those levels to the peripheral blood. Myelograms used initially to identify the CVF were evaluated for modality, CVF laterality, CVF level, and venous drainage pattern. Patient sex, patient age, and symptom duration were also collected. Brain MR images were reviewed for Bern scores. We also measured the peripheral blood BTP levels in 20 normal controls.

RESULTS: In patients with CVF, the mean BTP level near the CVF was 54.5% higher (0.760 [SD 0.673] vs 0.492 [SD 0.095] mg/L; $p = 0.069$) compared to peripheral blood. Nine (64.3%) patients with CVF had a higher paraspinal BTP level than peripheral BTP level. The 20 control patients had a higher the mean peripheral BTP level 0.720 (SD 0.191) mg/L compared to patients with CVF ($p < 0.001$).

CONCLUSIONS: We found that venous blood at the site of CVF had higher BTP values compared to peripheral blood in the majority, but not all patients with CVF. This may reflect the intermittent leaking nature of CVF. Additionally, we found that patients with CVF had a lower peripheral blood BTP level compared to normal controls. BTP requires further evaluation as a potential CVF biomarker.

ABBREVIATIONS: SIH = Spontaneous Intracranial Hypotension; CVF = CSF-Venous Fistula; CTM = CT myelogram; DSM = Digital Subtraction Myelography; BTP = Beta Trace Protein.

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From the Department of Radiology (I.T.M., W.B., J.T.V., J.C.B., A.A.M.), Department of Neurology (J.C.G.), and Department of Laboratory Medicine and Pathology (J.W.M.), Mayo Clinic, Rochester, MN, USA.

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Please address correspondence to Ian T. Mark, MD, Department of Radiology, Mayo Clinic, 200 1st St SW, Rochester, MN, 55905, USA; mark.ian@mayo.edu.

SUMMARY SECTION

PREVIOUS LITERATURE: CSF-venous fistulas are occult on conventional CT and MRI, and require an invasive myelogram for diagnosis. While clinical symptoms and brain MRI findings can suggest a spinal CSF leak, further development of objective data to help guide patient management is needed.

KEY FINDINGS: We found that the majority, but not all patients with CVF had higher beta trace protein (BTP) levels in the venous blood at the site of CVF compared to peripheral blood. This may reflect the intermittent leaking nature of CVF. Additionally, we found that peripheral blood BTP levels were lower in patients with CVF compared to normal controls.

KNOWLEDGE ADVANCEMENT: This study presents the use of BTP as a potential biomarker for CVF.

INTRODUCTION

Spontaneous intracranial hypotension (SIH) can present with debilitating but non-specific symptoms such as headaches, dizziness, and behavioral changes overlapping with frontotemporal dementia.¹ While numerous brain MR imaging findings are associated with SIH^{2,3}, up to 20% of SIH patients can have normal brain MR imaging⁴. CSF-venous fistulas (CVF), abnormal connections between the spinal CSF and a paraspinal vein, are now recognized as a major cause of SIH. Unfortunately, CVF are occult on conventional CT and MR imaging and require specialized myelography for detection⁵⁻⁹.

The absence of a reliable SIH biomarker presents two main diagnostic dilemmas. First, given the non-specific symptoms and oftentimes subtle brain MR imaging findings, many patients with SIH are undiagnosed. Conversely, invasive myelography is performed

in many patients who do not have a CVF or CSF leak found on the study. While myelography is a safe procedure, there is a risk of post dural puncture headache¹⁰ and iatrogenic abnormal brain MR imaging findings¹¹.

The underlying pathophysiology of a CVF dictates that CSF, normally contained within the thecal sac or nerve sheath diverticulum, escapes across an abnormal connection into the paraspinal venous system. A potential CVF biomarker would need to have the ability to detect CSF in the venous blood. Beta trace protein (BTP) is the second most common protein in the CSF after albumin and is the most abundant CNS derived protein in the CSF¹². The purpose of this study was to measure venous BTP level as a potential biomarker for CVF.

MATERIALS AND METHODS

Following IRB approval, we prospectively enrolled (May to September, 2023) patients with CVF identified on myelography. All myelograms were performed and read by a neuroradiologist in our spine intervention group who focuses on SIH. Each CVF was subsequently confirmed by an additional neuroradiologist who specializes in SIH (ITM). Myelogram details were recorded including modality, CVF laterality, CVF level, and venous drainage pattern. The electronic health record was reviewed for patient sex, patient age, and symptom duration. Pre-embolization brain MR imaging was reviewed for Bern scores.² All patients underwent transvenous catheter embolization for treatment of their CVF (Fig. 1).¹³ During the procedure, but prior to embolization, we attempted to take two venous blood samples (1-2 cc each) near the CVF. The first sample of venous blood was taken from a radicular vein at the level of the CVF. Given the complex paraspinal venous anatomy and CVF drainage, the azygos vein 1-2 vertebral bodies downstream from where the CVF was sampled. Generally, venous blood was collected from a radicular vein first, followed by the azygos vein, followed by the peripheral blood. The higher BTP value between the paraspinal vein and azygos vein samples was used as the CVF blood sample.

An additional sample of venous blood was collected from the groin access site as the peripheral blood sample. All venous samples were tested for levels of BTP using nephelometry.¹² Venous BTP gradients (BTP level of the blood near the CVF divided by the BTP level in the peripheral blood), were compared by CVF laterality (right versus left) and by level (upper cervicothoracic versus lower thoracic spine).

Peripheral venous blood samples were also tested for BTP in 20 normal controls. In addition to BTP, age and sex were recorded for the control population. Descriptive statistics in addition to basic analysis (mean, median, standard deviation) including p-value cutoffs of 0.05 were used for analysis.

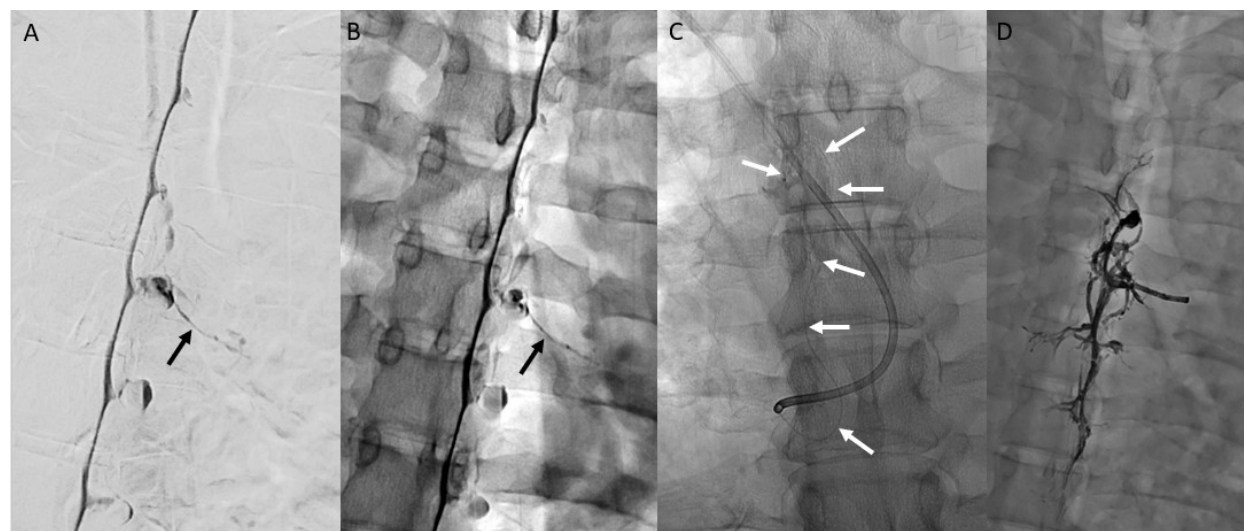


FIG 1. Patient with a right T5 CVF (black arrows) shown on DSM images (A, subtracted and B, unsubtracted). Procedural image during transvenous embolization (C) shows a guiding catheter in the SVC and azygos vein with a microcatheter (arrows) accessing the veins draining the CVF. Post-embolization image (D) shows the hyperdense Onyx cast.

RESULTS

14 patients with CVF were enrolled and had venous blood tested for BTP. Eight (57%) were female. The mean age was 58 years (range 40-71). Patient specific data including CVF laterality and level, as well as individual Bern scores, are listed in Table 1. The mean Bern score was 6 (range 0-9, median 8). The mean symptom duration was 29 months (range 1-168). Excluding one patient who had 14 years of symptoms, the mean symptom duration was 18 months.

The mean CVF BTP level was 0.760 mg/L (SD 0.673), which was 54.5% higher than the mean peripheral BTP level of 0.492 mg/L (SD 0.095) but not a statistically significant difference ($p=0.069$). Nine (64.3%) patients had a higher CVF than peripheral BTP level. Paraspinal venous blood was unable to be collected in 3 patients secondary to slow flow. Azygos blood was collected in all patients. In the 11 patients with venous samples from both radicular and azygos veins, the azygos vein had a higher BTP level in 6 patients (54.5%). This likely reflects the normal complexity of the paraspinal venous drainage system. One patient with a negative BTP gradient (peripheral BTP > CVF BTP) had complex CVF drainage including to a lateral muscular branch that was not sampled in addition to drainage to the

radicular veins and azygos system. The CVF drainage patterns were predominantly external vertebral venous plexus (EVVP) in 10 patients (71.4%) and predominantly internal vertebral venous plexus (IVVP) in 2 patients (14.3%). Two patients (14.3%) had mixed IVVP and EVVP drainage, one of which also involved a lateral muscular venous branch. Our sample size was too limited to draw conclusion regarding the venous drainage patterns and venous BTP levels.

There was no significant difference in BTP gradients between CVF that occurred at T6 and above compared to below T6 (mean 1.63 vs 1.35 mg/L, $p=0.64$), nor was there a difference between left and right sided CVF (mean 1.71 vs 1.33 mg/L, $p=0.60$). Patients with low probability brain MR imaging findings (Bern score <2) had a lower mean BTP gradient compared to high probability brain MR imaging findings (Bern score >5), 0.99 and 1.67 mg/L respectively, but this was not statistically significant ($p=0.15$).

Of the 20 control patients, 9 (45%) were male. The mean age was 47.9 years (SD 21.4). The mean serum BTP level was 0.720 mg/L (SD 0.191). The difference between the peripheral blood samples in the CVF patients and the control patients was statistically significant ($p<0.001$).

DISCUSSION

We measured venous BTP levels in patients with CVF and found that most but not all patients had higher BTP levels in veins near the CVF compared to the peripheral blood. Additionally, we measured peripheral venous blood in patients with CVF and found that they had lower BTP levels compared to normal controls. BTP is the most common CNS derived protein in the CSF and was therefore assessed as a biomarker for the presence of CSF in venous blood. Our work evaluated venous BTP level as a potential biomarker for CVF.

Beta-2-transferrin is the most common test used in the United States to confirm the presence of CSF in nasal or ear secretions in patients suspected to have a skull base CSF leak. There are several limitations that prohibit beta-2-transferrin from serving as a blood test for CVF. First, available beta-2-transferrin assays are not reliable in the presence of blood.¹⁴ Additionally, the commonly used test for beta-2-transferrin cannot detect low concentrations and is not quantitative.¹⁵ BTP, in contrast, is measured with nephelometry that can assess blood samples and quantify even low levels of the target analyte, and has been previously used to evaluate fluid for CSF otorrhea and rhinorrhea.^{12,15} While BTP is primarily a CNS derived protein, other organs including the heart, testes, and prostate have also been found to produce BTP¹⁶. Therefore, low levels of BTP in the peripheral blood are expected in patients who do not have a CVF. BTP can be systemically elevated in other conditions, including end stage renal disease¹⁷, of which none of our patients had.

The first purpose of our study was to evaluate venous BTP levels at multiple locations within a patient to see if CVF drive BTP levels that are different. We hypothesized that BTP, originating in the CSF, should be higher near the CVF compared to the peripheral blood, where it is less concentrated. Our study found that blood near CVF had a higher BTP concentration compared to peripheral blood in 64.3% of patients. The negative BTP gradient (higher BTP in peripheral blood) in the remaining patients could be due to slow or intermittent leakage of CSF. Our group has previously studied CVF temporal characteristics and found that CVF are intermittently seen on DSM¹⁸. Callen et al.¹⁹ performed a similar study using CTM and also found that CVF are intermittently seen. Therefore, the 35.7% of patients whose CVF BTP level was lower compared to peripheral blood could be due to lack of CSF leakage at the time of venous sampling. Resisted inspiration simultaneously increases CSF pressure while decreasing venous pressure²⁰ and has been shown to help visualize CVF on myelography²¹, but we did not provide patients with consistent breathing instructions during our study.

The second aim of our study was to determine if peripheral venous BTP levels in patients with CVF are different compared to normal controls. We anticipated that venous BTP, a CNS derived protein, would be elevated in patients with CVF compared to normal controls. We found that peripheral venous BTP levels had a statistically significant difference, however patients with CVF had lower BTP levels compared to normal controls. The reason for this is unknown. Recent work by Wolf et al^{22,23} has shown that patients with SIH have altered CSF flow at the level of C2-C3, with increased downward velocities. Our recent work²⁴ has also highlighted the downward craniocaudal CSF flow in spinal CSF leaks causing SIH, as possible differentiating factor from skull base CSF leaks. The altered CSF flow in SIH could conceivably pool BTP in the dependent lumbosacral spine. The CSF escaping through CVF, most commonly in the thoracic spine, could have lower BTP levels than normal states.

Our study had limitations, most notable being the small sample size. Our study measured BTP in only 14 patients with CVF and should be expanded upon in future studies. We included 20 control patients, however our mean BTP level of 0.720 (SD 0.19) mg/L was similar to previous studies that measured peripheral blood BTP: 0.69 (SD 0.33) mg/L²⁵, 0.59 (SD 0.23) mg/L²⁶, and 0.59 (SD 0.11) mg/L²⁷. Our study had additional limitations in that the normal controls did not have MR imaging or myelography to assess for findings of SIH or CVF, however they did not have a significant medical history to suggest SIH. A final limitation of the study includes the complex venous anatomy of the paraspinal veins. We cannot be certain that the radicular vein used for sampling was the primary drainage pathway for the CVF, and therefore we accounted for this by collecting blood from the azygos vein as well. Future directions to study would not only include a larger number of patients, but also assess the clinical significance of BTP levels related to patient symptoms, myelogram findings, and patient outcomes.

Table 1: Patient specific data organized by ascending BTP gradients.

CVF Side	CVF Level	Bern Score	Dx Modality	CVF BTP (mg/L)	Peripheral BTP (mg/L)	BTP Gradient	Symptom duration (mo)
L	T8	8	PCD-CTM	0.367	0.459	0.80	6
R	T6	0	DSM	0.571	0.631	0.90	4
L	T7	2	DSM/CB-CTM	0.496	0.544	0.91	24
L	T12	8	PCD-CTM	0.461	0.472	0.98	4
R	T4	4	PCD-CTM	0.397	0.397	1.00	60
R	T6	8	CB-CTM	0.534	0.503	1.06	21
R	T5	6	DSM	0.531	0.489	1.09	168
R	T7	6	EID-CTM	0.615	0.551	1.12	8
L	T9	1	PCD-CTM	0.476	0.414	1.15	36
L	C8	9	PCD-CTM	0.593	0.417	1.42	36
R	T7	9	PCD-CTM	0.480	0.291	1.65	1
R	T9	3	DSM	0.914	0.496	1.84	12
R	T8	8	DSM	1.240	0.627	1.98	8
L	T11	8	DSM/EID-CTM	2.960	0.595	4.97	12

CTM = CT myelography; DSM = Digital Subtraction Myelography; CB = Cone Beam; PCD = Photon Counting Detector; EID = Energy Integrating Detector

CONCLUSIONS

Our study measured venous blood BTP levels as a potential CVF biomarker. We found that 64.3% of patients had higher venous BTP levels near the CVF relative to the peripheral blood. The intermittent leaking nature of CVF may explain the lack of elevated BTP in blood near CVF in one-third of patients. Additionally, we found that patients with CVF had a lower peripheral blood BTP levels compared to normal controls. BTP requires further evaluation as a potential CVF biomarker.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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