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Advances in biomarkers for vasospasm – Towards a future blood-based diagnostic test

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ABSTRACT

Objective: Cerebral vasospasm and the resultant delayed cerebral infarction is a significant source of mortality following aneurysmal SAH. Vasospasm is currently detected using invasive or expensive imaging at regular intervals in patients following SAH, thus posing a risk of complications following the procedure and financial burden on these patients. Currently, there is no blood-based test to detect vasospasm.
Methods: PubMed, Web of Science, and Embase databases were systematically searched to retrieve studies related to cerebral vasospasm, aneurysm rupture, and biomarkers. The study search dated from 1997 to 2022. Data from eligible studies was extracted and then summarized.
Results: Out of the 632 citations screened, only 217 abstracts were selected for further review. Out of those, only 59 full text articles met eligibility and another 13 were excluded.
Conclusions: We summarize the current literature on the mechanism of cerebral vasospasm and delayed cerebral ischemia, specifically studies relating to inflammation, and provide a rationale and commentary on a hypothetical future bloodbased test to detect vasospasm. Efforts should be focused on clinical-translational approaches to create such a test to improve treatment timing and prediction of vasospasm to reduce the incidence of delayed cerebral infarction.

1. Introduction

Cerebral vasospasm is a complex pathologic process that is among the most detrimental after-effects of subarachnoid hemorrhage (SAH). SAH is the exposure of blood in the subarachnoid space that can result from several pathologic processes, such as hypertension, ruptured vascular lesions, hemorrhagic tumors, and trauma. Cerebral vasospasm can occur as segmental or diffuse narrowing of the cerebral vasculature.[1] Vasospasm can result in clinical deterioration caused by delayed cerebral ischemia (DCI). Over 30% of patients with ruptured aneurysms develop DCI and decreased neurologic status; therefore vasospasm is a condition that must be detected swiftly.[2]

A recent study found that the incidence of vasospasm is higher among those of lower socioeconomic status (SES).[3] Low SES patients are more likely to have comorbidities to promote aneurysm formation and increase the risk of rupture, which in turn increases the prevalence of vasospasm. Additionally, low SES patients are unlikely to access timely diagnosis or treatment to prevent rupture of their cerebral aneurysm.[3] The current standard of care (SOC) may place an undue financial burden with vasospasm following post-aneurysmal SAH.

Although there are methods for detecting vasospasm through various imaging modalities, many of the common techniques depend on operator capability and can be invasive. Others have lower overall accuracy and there is simply a gap in accurate & efficient diagnosis of vasospasm. This review article investigates the utility and potential of a blood-based diagnostic test to detect cerebral vasospasm and its severity in patients following SAH.

2. Methods

This Systematic Review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies related to cerebral vasospasm, aneurysmal rupture, and biomarkers were included. Titles and abstracts were independently screened to

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identify relevant studies. The following keywords were using in the initial search across databases to identify relevant publications: cerebral, vasospasm, spasm, aneurysm, biomarker, marker, signal, and diagnostic. The study search dated from 1997 to 2022. The literature search was performed on the PubMed, Web of Science, and Embase databases for relevant literature.

3. Results

Out of the 632 citations screened, 65.7% ($n = 415$) of records were excluded during title screening due to not being relevant (Fig. 1). Next, out of the remaining 217 abstracts, 72.8% ($n = 158$) were excluded during in-depth review: 122 did not report any biomarkers studied, 26 were case reports, and 10 were review articles. Out of the 59 full text articles that met eligibility, another 22% ($n = 13$) of citations were

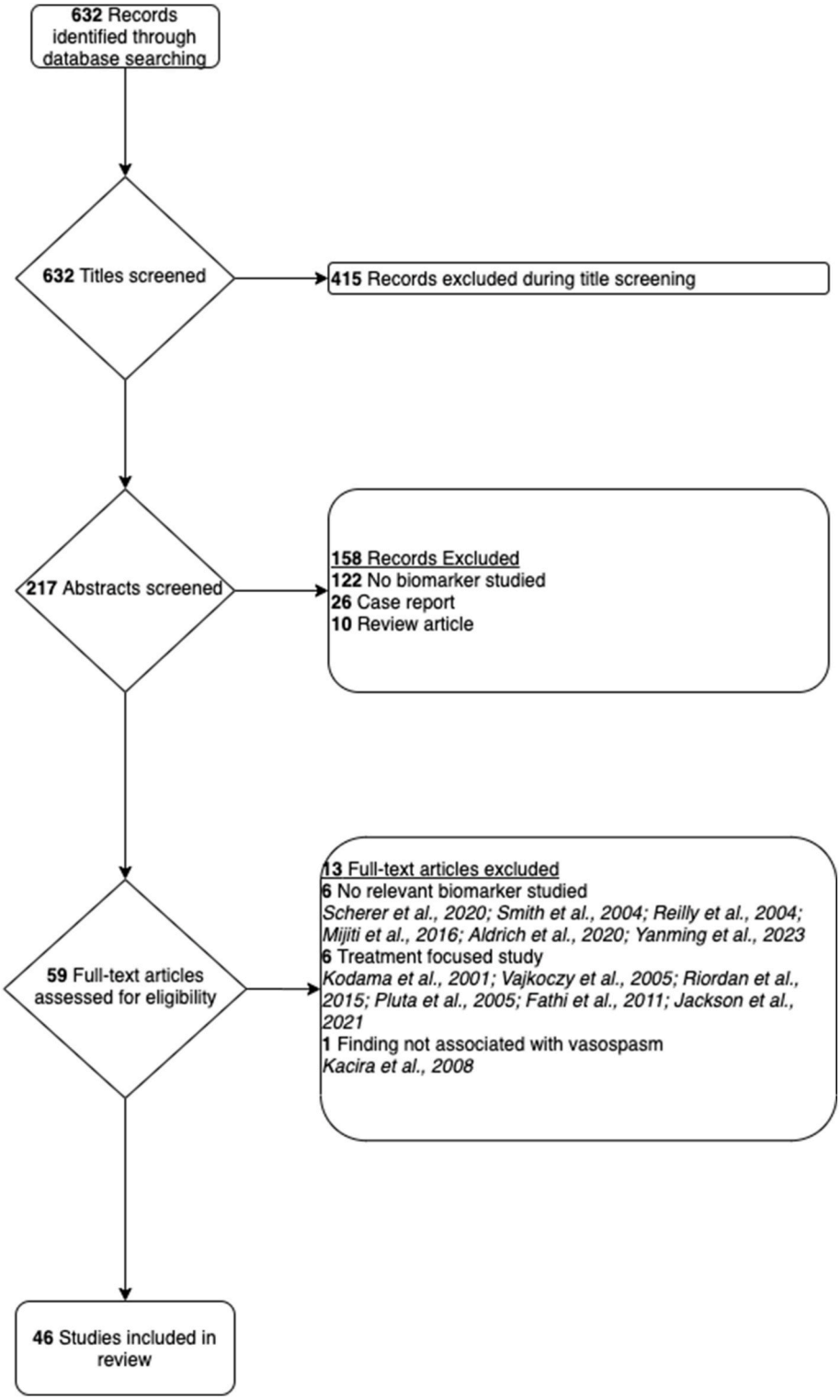

Fig. 1. PRISMA diagram.

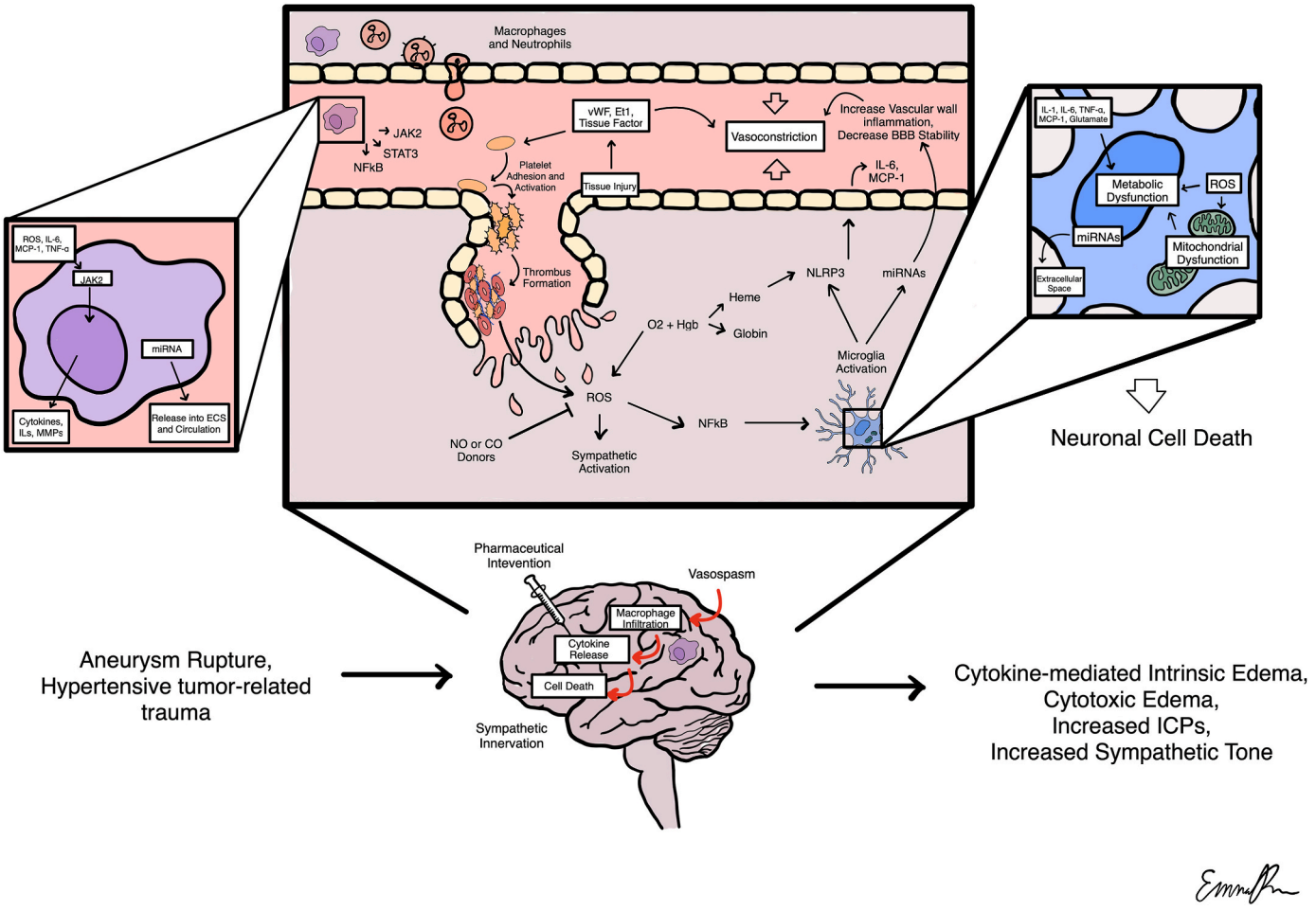

Fig. 2. Mechanism of inflammation mediated vasospasm following SAH. Aneurysm rupture, hypertensive tumor related trauma, or other causes lead to SAH. Following SAH, the development of vasospasm is precipitated by ROS, inflammatory cytokines, and toxic blood breakdown byproducts. Inflammatory cytokines namely, IL-6, MCP-1, and TNF-α act on macrophages resulting in the activation of JAK2, STAT3, and NFkB, which perpetuate further inflammation. Macrophages also release additional ILs and MMPs further contributing to vasospasm. The thrombus formed in the aneurysm subsequently creates ROS further activating the sympathetic nervous system and NFkB and contributing to metabolic and mitochondrial dysfunction in microglia. Microglia then release miRNAs further exacerbating vasospasm. Heme from hemoglobin then activates the NLRP3 inflammasome complex which acts on the endothelium to release IL-6 and MCP-1. Vasospasm ultimately leads to cell death through macrophage activation and cytokine release, which presents an opportunity for pharmaceutical intervention. Some interventions already explored are NO and CO donors which prevent the formation of ROS.

excluded: six had no relevant biomarkers studied, another six were treatment-focused, and one study reported findings not associated with vasospasm (see Fig. 2).

4. Discussion

4.1. Current advanced methods of diagnosing vasospasm

The primary method of diagnosing cerebral vasospasm is through a number of imaging modalities. Common techniques to diagnose vasospasm include digital subtraction angiography (DSA), computed tomography angiography (CTA), computed tomography perfusion (CTP), and transcranial Doppler (TCD) ultrasonography.[4] Additionally, regular neurological examinations can be used effectively for detecting symptomatic vasospasm.[5–7]

One of the most common methods of detecting vasospasm is with TCD, which uses ultrasound to quantify blood flow rate and direction in specific vessels. TCD relies on the concept that increased blood flow rate indicates narrowing of the vessel lumen.[8] TCD is non-invasive and poses minimal risk to the patient and is therefore commonly used. However, some limitations exist, including difficulty in localizing vessels and confounding factors that may alter blood flow velocity. Thus, TCD tends to be less accurate for detecting vasospasm than other methods.[9]

DSA is the gold standard to diagnose vasospasm. Although it is the most accurate diagnostic method, patients are at a higher risk of complications (5%), including stroke (1%).[10] DSA also allows for rapid and direct treatment if necessary. Balloon angioplasty and pharmacologic spasmolytics are both able to be used in combination with DSA, making this modality versatile, if not resource prohibitive, for management of vasospasm.[11] Despite DSA being the gold standard for vasospasm detection, it is an invasive procedure accompanied by elevated complication risks, and ties up vital hospital resources. Several studies have examined the viability of computed tomography angiography (CTA) as an alternative to DSA. Many studies report relatively high agreement values between CTA and DSA in detecting vasospasm, with different studies ranging from 83 to 95% agreement.[7,12] Thus, there is evidence that CTA can be used as a reasonable alternative to DSA, keeping in mind the risks of additional radiation exposure that CTA carries.

Another imaging modality used to diagnose cerebral vasospasm is Magnetic Resonance Angiography (MRA). While not as frequently used as DSA or CTA, MRA has been found to be viable in the diagnosis of cerebral vasospasm. An early study testing vasospasm detection in monkeys found that MRA and conventional angiography were equally

efficient in detecting vasospasm and that MRA even outperformed conventional angiography in demonstrating dilation of control arteries.[13] In patients, however, MRA has not been found to be as effective as conventional angiography, with MRA detecting only roughly 87% of conventional angiography vasospasm diagnoses.[14] Most clinical management guidelines for subarachnoid hemorrhage management recommend using DSA and TCD in cases of suspected vasospasm.[15]

Table 1 summarizes reported sensitivities and specificities of different modalities in detecting vasospasm. A simpler non-invasive method to detect vasospasm would improve patient outcomes and reduce healthcare costs.

4.2. Rationale for screening for vasospasm

It is imperative to screen for and accurately diagnose vasospasm, as untreated vasospasm can lead to devastating effects in patients following SAH. Of patients with cerebral vasospasm detected on radiography, roughly 25–30% are symptomatic and thus classified as having clinical vasospasm.[16,17] Overall, 10–45% of patients with SAH suffer clinical deterioration caused by delayed cerebral ischemia (CD-DCI).[18] A large multicenter study found that ischemic infarction resulting from vasospasm carries a significant mortality risk (23%).[19] In addition to the high mortality rate, vasospasm can lead to several morbidities including decreased self-rated health as scored by the EQ-5D visual analog scale, depressed mental status, lengthier hospital stay, and persistent coma.[20] The high incidence of vasospasm following SAH warrants cost-efficient and simple screening to detect vasospasm to best optimize treatment timing.

It is important to note, however, that the links between vasospasm and ensuing neurologic deficits are not completely clear. For instance, the CONSCIOUS-1 trial (a randomized, double-blinded, placebo-controlled study examining the safety and efficacy of clazosentan) shed light on whether vasospasm is the primary cause of DCI. The main reason for this doubt was that clazosentan was found to decrease vasospasm occurrence but DCI rates were not affected.[21,22] Additional studies point to the idea that other factors combine to contribute more to DCI occurrence independent of vasospasm, including arteriolar constriction & thrombosis, cortical spreading ischemia, and others.[23] Early brain infarction was also found to be a significant factor in CD-DCI.[24]

4.3. Inflammatory pathways in vasospasm/pathophysiology of vasospasm

Over the last few decades, the literature examining cerebral vasospasm studied biomarkers ranging from hemoglobin breakdown products to inflammatory cytokines (see Fig. 2).

Numerous studies have investigated specific proinflammatory molecules as potential causative agents of vasospasm. While each of these substances have shown causative properties in a portion of cerebral vasospasm cases, no single proinflammatory factor has been found to be the root of all vasospasm–which speaks to the tremendous heterogeneity of the pathology.[25] Formation of microthrombi as a result of macrophage activation and consequent cytokine release (interleukins, TNF-α, and reactive oxygen species (ROS) has also been implicated in vasospasm. These cytokines and inflammatory agents then activate adhesion molecules leading to the platelet activation cascade and leukocyte activation. Specifically, P-selectin and E-selectin have been found to be upregulated in patients with ruptured cerebral aneurysms.[26–28] Furthermore, patients who developed DCI were found to be more hypercoagulable in comparison to patients who did not develop DCI following SAH.[29,30] Matrix metalloproteinases (MMPs) are also released from immune cells, namely macrophages and leukocytes, as a result of inflammatory cytokine activity.[31] Upon activation, MMPs can lyse other pro-MMPs into MMPs, leading to a positive feedback loop. Cellular migration is promoted as MMPs destroy the extracellular matrix, leading to increased inflammation and cytokine production and eventually contributing to vasospasm.[32] A variety of MMPs have been implicated in vasospasm; however, MMP-9 was found to be a key agent of degradation of the basal lamina contributing to blood–brain barrier dysfunction.[33] Preclinical studies have found MMP-9 knockout mice exhibit better neurological recovery, less brain edema, and lower chronic intracranial pressure compared to wild type mice following induction of SAH.[33] Furthermore, human serum samples among patients with SAH were found to have significantly lower levels of MMP-2 and elevated levels of MMP-9, suggesting both MMP-2 and MMP-9 may be potential biomarkers of vasospasm.[34,35]

The presumed mechanism of vasospasm is increased chemotaxis and transmigration of the myeloid and monocyte cell subsets into the local vascular environment, thus leading to increased vasoconstriction. Upon early brain injury, various markers of apoptosis and necrotic cell death have been observed, including danger signal high-mobility group box 1 (HMGB1), IL-6, and TNF-α.[36–38] Neuronal death decreases basal metabolic rate and increases permeability of the blood brain barrier. Metabolic dysfunction further promotes cell necrosis leading to exacerbated inflammation. Dying neurons release various signals that continue to drive inflammation following SAH.[39] Increased intracranial pressure and edema exacerbate metabolic dysfunction. Mitochondrial dysfunction has been associated with SAH patients and leads to increased tissue sensitivity, likely contributing to vasospasm.[40] Astaxanthin is a therapeutic that reduces mitochondrial dysfunction and has been found to decrease cerebral vasospasm in animal models following SAH.[41] Cerebrospinal fluid analysis from patients with SAH accompanied by DCI revealed increased autophagy and mitophagy as a result of mitochondrial dysfunction.[42]

Macrophage and monocytes are the primary effector cells responding to SAH. Although these cells have not been studied extensively in relation to vasospasm, increases in monocytes have been observed in the 1–2 days following SAH.[43] Groups have also demonstrated infiltration of macrophages no sooner than 3 days following SAH in the brain parenchyma suggesting a role macrophages play in vasospasm.[44]

Upon macrophage activation, nuclear transcription factors such as NF-kB and STAT3 are activated, resulting in further propagation of inflammation.[45,46] Endothelin-1 (ET-1), von Willebrand Factor (vWF), and tissue factors released from the injured endothelium contribute to platelet activation and adhesion and increased vasoconstriction.[47–49] Cytotoxic blood byproducts (bilirubin, biliverdin, and heme) contribute to increased ROS formation, further exacerbating microglial activation through NF-kB.[50] Heme and heme breakdown products upregulate NLRP3 acting on the endothelium via cyclooxygenase (COX)-1 and COX-2 pro-inflammatory eicosanoids, leading to release of IL-6 and MCP1, contributing to additional vasoconstriction.[51–53]

Oxidative stress and endothelins may also be linked to vasospasm with studies showing their elevation in patients with post-SAH vasospasm.[25] ET-1 has been implicated in pulmonary hypertension contributing to increased pulmonary vascular resistance.[54] In-vivo animal testing has found ET-1 to be a potent cause of vasoconstriction through its effect on pulmonary vascular smooth muscle. Activation of the sympathetic nervous system has also been implicated in the development of vasospasm. Multiple groups have successfully alleviated vasospasm following SAH by blocking the sympathetic nervous system using stellate ganglion block.[55,56] Preclinically, activation of the sympathetic

Table 1
Sensitivity and specificity of diagnostic techniques to detect vasospasm. *Sensitivity and specificity may vary depending on radiologist.

Diagnostic Technique	Sensitivity	Specificity
DSA (gold standard)	100%*	100%*
CTA (PMID: 34970916)	31%	81%
TCD (PMID: 2682350)	100%	59%
MRA (PMID: 36357992)	84%	72%
CT perfusion (PMID: 17416833)	20%	100%

nervous system has been found to decrease cerebral perfusion in swine. Activation was found to be inhibited by anesthetic injection prior to sympathetic activation.[57] Blockade of the sympathetic nervous system could be a promising treatment target for vasospasm following SAH.

4.4. Potential blood biomarkers for vasospasm

Various blood biomarkers have been studied to predict vasospasm. Despite ongoing research, candidate biomarkers have not been specific to vasospasm, thus having low clinical utility. Early biomarkers of interest include neutrophil products, leukocyte products, and creatinine as measurables that could aid in diagnosis.[58]

Biological microparticles are small extracellular vesicles released by various nuclear and anuclear components of the blood system including erythrocytes, leukocytes, and platelets.[59] Endothelial cells also produce microparticles, and these vesicles are important for regulation of endothelial stress and dysfunction.[60] Microparticles, composed of cellular membrane components from membrane budding, have a variety of roles and identities, including functions in cellular processes such as inflammation, oxidative stress, injury, etc.[61] Sanborn et al found that aneurysmal SAH patients had elevated levels of endothelial microparticles in blood, suggesting a potential role for microparticles in the signaling process of SAH and eventually vasospasm.[62] However, candidate microparticles have not been validated clinically.

Endothelin-1 (ET-1) is a small peptide released by endothelial cells of the vascular system. It is one of the principal molecules responsible for vasoconstriction and has been hypothesized to play a role in vasospasm post-aneurysmal SAH.[63] The suggested mechanism is that degradation of hemoglobin and oxidative stress from SAH prompts the release of ET-1 by vascular endothelial cells.[64] Several studies have examined the biomarker potential of ET-1 in vasospasm. In particular, a study by Bellapart, et al reported that plasma levels of ET-1 were substantially higher in SAH patients with vasospasm than in those without.[65] There was no marked change in cerebrospinal fluid (CSF) levels of ET-1 in this study, indicating that ET-1 may be better used as a blood biomarker than in CSF.

Panels of microRNAs have also been studied as potential biomarkers of vasospasm. Of the miRNAs studied, miRNA-24 upregulation has been found to cause vasospasm and is believed to suppress nitric oxide synthase (NOS), as nitric oxide metabolism has been found to have an inhibitory effect on vasospasm occurrence.[66,67] A miRNA panel studying 442 miRNAs in patients with aneurysmal SAH reported hsa-miR-3177-3p to be significantly elevated in patients with vasospasm.[68] When used in combination with each other, miRNAs have improved predictive potential. A panel of 47 specifically selected miRNAs tested in 31 patients following SAH and 8 healthy controls reported an accuracy of 87% in predicting vasospasm.[69]

Similarly, a study evaluated an mRNA panel on SAH patients to understand if there is differential expression between those who develop vasospasm and those who do not. They found that there were 259 differentially expressed genes in vasospasm patients. Important differentially expressed pathways included adrenergic, nitric oxide, and thrombin.[70] A different study performed serial analysis of different serum protein levels on vasospasm patients using quantitative analysis. The proteins that decreased significantly in concentration in vasospasm patients were alpha-2-macroglobulin, angiogenin, apolipoprotein A-IV, granulocyte colony-stimulating factor, macrophage-stimulating protein, tetranectin, and VEGF receptor 3. The only protein that increased out of this assay was vitronectin.[71]

There are numerous other serum proteins that have shown associations to cerebral vasospasm presence. A study found that soluble Fms-like tyrosine kinase 1 (sFlt-1) was found to be increased in SAH patients who were high risk for vasospasm, and no correlation between soluble endoglin and vasospasm.[72] Another novel molecule that was shown to be significantly elevated following SAH and in patients who developed cerebral vasospasm was Systemic High-Mobility Group Box-1.[73] Serum myeloperoxidase (MPO) was also significantly increased in vasospasm patients, as it was elevated prior to vasospasm in 67% of cases and on the day of vasospasm in 53% of cases.[74]

Kula et al, 2023 with a cohort of 96 patients found that neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), and system inflammatory index (SII) all had some clinical relevance. Specifically, NLR showed a significant difference on the seventh day, dNLR on days 2, 4, and 9, and SII on day 9.[75] A different study using SII found similar results in which the SII analysis predicted vasospasm accurately (area under the curve = 0.767 & $p < 0.001$).[76] General leukocytosis has also been found to be an independent risk factor for vasospasm following SAH.[77]

Table 2 summarizes all blood biomarkers found in association with vasospasm in humans or preclinical animal models from a comprehensive search on PubMed.

4.5. CSF biomarkers for vasospasm

In addition to blood biomarkers, CSF products have also been studied as potential biomarkers of cerebral vasospasm. Although many molecules may show promise by displaying correlations with vasospasm, there has still not been a single biomarker discovered that can definitively diagnose or predict vasospasm.

Various metal ion concentrations in CSF may be associated with vasospasm occurrence, as iron levels were significantly elevated during days 7–10 after SAH and zinc concentrations were elevated from days 11–14. Sodium, calcium, magnesium, and copper concentrations did not show any correlations.[78]

α-II spectrin is a member of the spectrin protein family, whose proteins are present in the cytoskeleton and are involved in intercellular communication, cell-regulation, etc.[79] α-II spectrin is primarily found in cardiac muscle, although it has been shown to be a useful biomarker of many different types of injury and disease, including in the nervous system.[80] Lewis et al found that α-II spectrin breakdown products (SBDPs) levels were significantly elevated in the CSF of vasospasm.[81] It is worth noting that cerebral vasospasm was diagnosed in these patients through neurological exams and GCS, so a correlation with SBDPs can only be made with clinical vasospasm.

Siman et al revealed a panel of biomarkers typically involved in neurodegeneration and their potential to predict cerebral vasospasm.[82] The study found 6 proteins upregulated in the vasospasm patients, including CCSctf, 14-3-3b, UCHL1, 14-3-3ζ, CCSntf, and Neuron Specific Enolase (NSE). These proteins, however, were upregulated at different time points, up to day 10 after SAH. These findings suggest that a unique biomarker fingerprint composed of various biomarkers may be necessary to best diagnose vasospasm.

NSE is an enzyme with multiple functions in the nervous system. It is expressed in the cytoplasm of neurons and moves to the cell surface to respond to pathologies such as injury, infection, and cancer, making it a good biomarker to detect various pathologies in the brain.[83] Thus, NSE is not specific to vasospasm and may also be upregulated in traumatic brain injury and ischemic stroke.

Biomarkers that arise from altered metabolism of neurons have also been studied as potential biomarkers for cerebral vasospasm. In particular, the glutamine and glutamate cycle has been suggested to be a potential marker of cerebral vasospasm. Glutamine is taken up by neurons where it is converted to glutamate, energy being derived from this process.[84] Because vasospasm restricts blood flow, metabolism tends to also decrease intracerebrally. It has been found that there was a correlation between CSF levels of glutamine, glutamate, histidine, and glycine and cerebral vasospasm occurrence.[85] Since metabolism decreases in cerebral ischemia, higher glutamine levels were correlated with vasospasm.[61]

As vasospasm does not affect all patients following SAH, some researchers have suggested a genetic predisposition to developing vasospasm. One protein that has been studied numerous times as both a potential CSF biomarker and a genetic link to cerebral vasospasm is

Table 2
Reported biomarkers of cerebral vasospasm.

Biomarker	In-Vivo Animal Study	Human Blood Samples	Human CSF	Study	PMID
Haptoglobin 2-2 gene polymorphism		x		Leclerc et al 2015, Ateia et al 2020	25583472 33069930
ApoE4 gene polymorphism		x		Wu et al 2011	21116929
219T ApoE promoter polymorphism		x		Wu et al 2010	20868652
NSE			x	Simal et al 2011	22174930
UCHL1			x	Siman et al 2011	22174930
pNF-H		x	x	Lewis et al 2008	18319731
SBDP			x	Lewis et al 2007	17937225
ICAM-1 and VCAM-1		x	x	Kim et al 2013	24297765
TNF-α		x	x	Chou et al 2012	22918199
CRP		x	x	Fountas et al 2009	19409001
Amino acids			x	Jung et al 2013	19743467
ApoE			x	Alexander 2008	18829593
Endothelin-1		x	x	Bellapart et al 2014	23921571
Calcium			x	Alexander et al 2008	18829593
Nitrite/nitrate			x	Lin et al 2006	16631536
hematological microparticles		x		Sanborn et al 2012	22794324
CD105-labeled endothelial microparticle		x		Lackner et al 2010	20814009
SOD	x				12574556
IL-6			x		27931942
MMP-2		x			17087971
MMP-9		x			17087971 27504251 12383357
miRNA-24		x	x		29845232 34055880
hsa-miR-3177-3p		x			30354977
miRNA-126		x			35836862
Arginase-1			x		34599427
Lp-PLA2		x			32922938
Tissue kallikrein		x			31866331
S1PR4 mRNA		x			31783362
Glucose-Potassium ratio		x			31060790
High-Mobility Group Box 1		x			28189859
S100B		x	x		23761779
autophagy and mitophagy markers (DAPK1, BNIP3L, BAX, PINK1, ULK1, and NDP52)			x		34389795
Myelin basic protein			x		11680510
Membrane-bound tissue factor			x		11680510
Histidine-rich Glycoprotein			x		30820052
Leukocytosis		x			12816268
MIF			x		31585427
Neutrophil-to-lymphocyte ratio		X			37634893
Soluble FMS-Like Tyrosine Kinase 1		X			28867315
High-Mobility Group Box-1		x			30028365
Systemic Immune-Inflammation Index		x			37634893
Metal ions			X		25366601
Myeloperoxidase		x			22370810
Neuropeptide Y			X		23915659

Apolipoprotein E (APOE).[61] APOE normally plays a role in fat metabolism, as it transports cholesterol and other lipids into the bloodstream.[86] When CSF APOE levels are decreased, it has been shown that the vascular endothelium is affected, leading to alteration of vascular relaxation mechanisms. Alexander et al reported a correlation between lower levels of APOE and cerebral vasospasm occurrence, although there was no distinction between clinical and radiographic vasospasm.[87] This supports the idea of APOE affecting vascular endothelium and thus potentially predicting vasospasm occurrence, as there was no correlation between APOE and cerebral ischemia resulting from vasospasm. In separate studies, a genetic link between patients expressing the apoE ε4 allele and cerebral vasospasm following SAH was found, further supporting the potential link between functional APOE levels and cerebral vasospasm.[88]

There are several other proteins that have shown possible links to vasospasm occurrence. One is macrophage migration inhibitory factor (MIF). MIF has been found to be significant elevated throughout the inflammatory process following SAH, as Kwan et al, 2019 reports significant elevation of MIF concentrations in aSAH patients, onset of clinical vasospasm, and evidence of DCI.[89] Another study evaluated membrane-bound tissue factor (mTF) and myelin basic protein (MBP) in relation to vasospasm. It was found that CSF levels of mTF showed correlation with vasospasm occurrence and recovery and CSF MBP levels were predictive of brain damage from vasospasm. A study evaluating the biomarker potential of histidine-rich glycoprotein (HRG) in CSF reported a significant difference in HRG levels between vasospasm and non-vasospasm groups.[90] Neuropeptide Y (NPY), a vasoconstrictive protein, has also been evaluated for its link to vasospasm. It was found that NPY levels were significantly higher in the CSF of vasospasm patients. Furthermore, non-vasospasm patients saw NPY levels gradually decrease whereas vasospasm patients had continually increasing NPY levels.[91]

Ultimately, any potential diagnostic tests utilizing CSF biomarkers will suffer from several factors limiting its wide use. First, the requirement for frequent CSF sampling may predispose the patient for higher infection risk or may require repeat lumbar punctures in absence of an external ventricular drain. Second, differences in the extent of subarachnoid hemorrhage, especially intraventricular hemorrhage may lead to confounding results with respect to specific biomarkers present. Table 2 summarizes all CSF biomarkers found in association with vasospasm in humans or preclinical animal models from a comprehensive search on PubMed.

4.6. Role for hybrid-biomarker blood test

It is well known that diagnosis and classification of vasospasm risk for individual patients is a complex and multifactorial process. Other diagnostic methods have been explored as a means of improving the

specificity and efficiency of diagnosis. In particular, machine learning modeling and statistical regression analyses (using variables such as vital signs, genetic makeup, cellular products, etc.) have great potential to be used for vasospasm detection.[92] Tanioka et al, 2019 that used both clinical and plasma values of MCP in their inputs produced a random-forest machine learning model with 95.1% accuracy, although detection of vasospasm was lower than this. Specifically, the most relevant ($P < 0.200$) clinical variables and biomarkers the model was trained on include sex, Osteopontin levels, Periostin levels, presence of cerebral contusion, and spinal cerebrospinal fluid damage.[93] These variables may be of particular interest for any future machine-learning based diagnostic test for vasospasm detection. A different study published in 2023 created an extreme-gradient-boost machine learning model to detect DCI but received sensitivity and specificity values of 33% and 74%, respectively–indicating a need for further refinement to make clinically useful models.[94]

Furthermore, other pathologies and conditions have begun to be correlated with non-traditional biomarkers that may be helpful for vasospasm diagnosis, such as certain bacteria flora in mycotic aneurysms and genetic markers in traumatic brain injury.[95–97] Obtaining different biodata from patients to enter into a hypothetical vasospasm-diagnostic model may require additional samples or data to be collected from patients, which may complicate adoption of a hybrid test.

4.7. Other non-invasive imaging

Over the last several years, there have been improvements made to the current standard of diagnosing cerebral vasospasm through non-invasive imaging. One technique that has been recently studied for its use in vasospasm diagnosis is Magnetic Resonance Angiography (MRA). MRA is a non-invasive imaging tool that has historically been used to image cerebral blood vessels. Malinova et al evaluated the use of MRA on a vasospasm model of rats.[98] It was found that MRA was able to accurately and noninvasively diagnose vasospasm in the rats and was able to identify the severity of vasospasm, with the researchers being able to make distinctions between moderate, mild, and severe vasospasm. Furthermore, a link was identified between severe MRA-detected vasospasm and ischemic lesions, indicating that MRA can potentially be used to predict DCI and symptomatic vasospasm. The most common form of MRA used for vasospasm detection is Time of Flight sequence (TOF) MRA.[99] Grandin et al evaluated the use of MRA in humans for vasospasm detection and found an overall sensitivity and specificity of 92% and 98%, respectively.[100] However, in certain arteries, namely the ICA and MCA, MRA could not be reliably used to diagnose vasospasm. While MRA is a viable technique, DSA remains superior.[100] With advances in MRA technology, MRA may serve as a reliable replacement for DSA.

Another detection technique that more-so focuses on diagnosing the dangerous downstream effect of cerebral vasospasm, delayed cerebral ischemia, is Computed Tomographic Perfusion (CTP). A study that examined 27 aneurysmal SAH patients found that when comparing CTP to DSA in diagnosis of vasospasm, there was a sensitivity of 90–95% and a specificity of 91–100%.[101,102]

4.8. Obstacles in creation of a blood-based diagnostic test for vasospasm

Many obstacles exist in the creation of a blood based diagnostic test for cerebral vasospasm. As mentioned earlier, the lack of specificity pertaining to any single biomarker studied currently poses a significant problem when attempting to create a blood based diagnostic test. Based on current literature, description of CSF biomarkers appears to be more prevalent compared to blood-based biomarkers. CSF biomarkers could be easily tested for in patients with an external ventricular drain, but in those without CSF diversion, they could prove a disadvantage. Clinician comfort with the strengths and limitations of current imaging modalities (DSA/CTA/MRA) may lead to hesitancy in adoption of a blood based diagnostic test. Furthermore, in-hospital laboratories may also be resistant to including the blood based diagnostic assay into their current paradigm. To the author's knowledge there are no cost-analyses currently measuring the efficacy and cost-savings of a hypothetical blood test compared to the standard of care. A large prospective study in human patients assessing the utility of various blood biomarkers is required to assess the feasibility of a blood based diagnostic test for the detection of cerebral vasospasm.

4.9. Ideal characteristics of a future blood test

Current efforts in narrowing down potential biomarkers to detect cerebral vasospasm and potentially delayed cerebral ischemia have not been successful. The difficulty in developing a test can be attributed to the lack of specificity in a single biomarker. To remedy these problems an ideal blood test should utilize a combination of biomarkers to predict vasospasm occurrence. As more biomarkers are included, the accuracy of the test could potentially increase. However, the price of the test will also increase as more biomarkers are included. Therefore, the number of biomarkers included in the diagnostic test should balance accuracy and cost effectiveness verified by a cost-analysis compared to standard diagnostic methods. An ideal diagnostic test would be simple to administer and use an easy to access patient sample with simple storage methods and limited sample preparation to ease integration into the existing in-hospital laboratory workflow. Lastly, the blood test should be able to produce a result on par with the current standard diagnostic methods on the order of hours. Therefore, this test must be a hospital administered test instead of a laboratory developed test that is sent to an external facility for processing. Of course, a positive test result would not obviate the need for advanced imaging to determine the location and extent of vasospasm as well as further clinical course.

5. Conclusions

Cerebral vasospasm is an incredibly dangerous complication following cerebral aneurysm rupture and subsequent subarachnoid hemorrhage. Although detection currently involves imaging modalities and neurologic examinations, these methods tend to be inefficient and expensive. Thus, a hybrid diagnostic test that uses a combination of biomarkers to detect vasospasm is needed. This diagnostic test would most likely be in the form of a blood-based test, as this would be the ideal combination of accuracy, cost, and efficiency. Although there is no clear biomarker for vasospasm detection that a test can be formed around, research trends are pointing at a few candidate molecules that may even be used in combination to detect and possibly quantify vasospasm risk. Future studies should look to understand cost-efficiency and economic impact of a hypothetical hybrid blood-based diagnostic test on the US healthcare system.

Founding sources

None.

CRediT authorship contribution statement

Aditya M. Mittal: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Kamil W. Nowicki:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Rohit Mantena:** Writing – original draft, Formal analysis. **Catherine Cao:** Writing – review & editing. **Emma K. Rochlin:** Visualization. **Robert Dembinski:** Writing – original draft, Data curation. **Michael J. Lang:** Supervision. **Bradley A. Gross:** Supervision. **Robert M. Friedlander:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

Clinical deterioration due to delayed cerebral ischemia: CD-DCI
Cerebrospinal Fluid: CSF
Computed Tomography Angiography: CTA
Computed Tomography Cerebral Perfusion Analysis: CTP
Delayed Cerebral Ischemia: DCI
Digital Subtraction Angiography: DSA
Glasgow Coma Scale: GCS
Intracranial Pressure: ICP
Magnetic Resonance Angiogram: MRA
Subarachnoid Hemorrhage: SAH
Socioeconomic Status: SES
Standard of Care: SOC
Transcranial Doppler: TCD