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Precision Medicine of Aneurysmal Subarachnoid Hemorrhage – Vasospasm and Delayed Cerebral Ischemia

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Abstract

Introduction—Precision medicine is an emerging paradigm aimed at providing individualized prevention and treatment of diseases through understanding and leveraging patient-to-patient variation. Aneurysmal subarachnoid hemorrhage (aSAH) carries tremendous morbidity and mortality with subsequent cerebral vasospasm (CV) and delayed cerebral ischemia (DCI) proving devastating and unpredictable. The paucity of effective treatment or prevention measures for these conditions could potentially be improved through implementation of precision medicine.

Areas covered—This review presents the basic pathophysiology of CV and DCI, current treatment guidelines, and evidence for the use of precision medicine in the prediction and prevention of poor outcomes following aSAH. An extensive PubMed literature search was performed using keywords cerebral vasospasm or delayed cerebral ischemia and either biomarkers, precision medicine, metabolomics, proteomics, or genomics. Over 200 peer-reviewed

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articles were reviewed. The studies presented focus on biomarkers identified as predictive markers or therapeutic targets following aSAH.

Expert Commentary—The array of novel biomarkers reviewed here, ranging from genotypes to metabolites, has been found to correlate with CV, DCI, and neurologic outcomes after aSAH. Though their practical use in the clinical management of aSAH is not well established, using these biomarkers as predictive tools or therapeutic targets demonstrates the potential of precision medicine in the treatment of aSAH.

Keywords

precision medicine; omics; subarachnoid hemorrhage; vasospasm; delayed cerebral ischemia; critical care; genomics; proteomics; metabolomics

1. Introduction

A movement toward Precision Medicine, defined by the National Academy of Sciences as the “tailoring of medical treatment to the individual characteristic of each patient”, promises to bring a more effective and personalized approach to patient care [1]. The Precision Medicine Initiative was announced by the United States Government in 2015, enhancing exposure of this national and international goal [1]. Precision medicine was already effectively in place in many medical specialties, such as oncology for tailoring chemotherapy and cardiology for risk stratification; however, recent biotechnological strides have allowed a more thorough understanding of disease processes and have also led to lower cost of the primary tools used in precision medicine, such as genomic sequencing [2].These “omic technologies”, including elucidation of an individual’s proteome, metabolome, microbiome, and epigenome, are key in advancing the practice of Precision Medicine [3]. The previous focus on applying Gaussian-curve statistics from population data to diagnose and treat disease is evolving to an approach that not only considers phenotypic subtypes, but also individual variances, down to the molecular level.

In the following article, we review the advancements made in the treatment of aneurysmal subarachnoid hemorrhage (aSAH), both currently available and on the horizon. Aneurysmal subarachnoid hemorrhage, comprising 2 to 5% of strokes, is one of the deadliest stroke subtypes with mortality reaching as high as 40% [Suarez, 2006 & Brott, Broderick, 1994]. In addition, morbidity from this devastating disease is significant with immediate neuronal damage and a high risk of DCI due to cerebral vasospasm (CV) and neurotoxicity [4]. It is estimated that 30,000–46,000 people a year suffer from aSAH in the US [5]. The treatment of aSAH is limited as there is only one FDA-approved medication to reduce DCI after aSAH, nimodipine. Wide variability of efficacy of this pharmaceutical agent has been seen in patients. Recent studies have shown lower cerebrospinal fluid (CSF) levels of nimodipine in those who suffered CV suggesting that individual differences in metabolism alter the efficacy of this treatment [6]. Neurointerventional routes can be effective in reducing CV and subsequent DCI; however, these interventions are typically initiated only after the patient becomes clinically symptomatic from the ischemic process or after ancillary testing, such as transcranial doppler (TCD) or CT-angiogram, indicate the presence of CV. Augmentation of cerebral perfusion pressure (CPP) is another important goal of treatment;

however, phenotypically there is a variable response to one specific CPP goal. In addition to these current treatment modalities, the Precision Medicine approach will be most useful in optimizing patient outcomes in the face of aSAH. This includes determining what we have called an individualized “omic signature” that utilizes genetic screening, use of biomarkers to stratify risk of developing delayed cerebral ischemia (DCI) after aSAH, phenomic cross-matching, development of individualized goals for physiologic metrics using multimodal monitoring (MMM), metabolomic assessment to optimize targeted therapy, and use of biomarkers for prognostication.

2. The Current State of the Art – Pathophysiology and Tools for Prevention and Treatment of Cerebral Vasospasm and Delayed Cerebral Ischemia

2.1 Pathophysiology

The primary deleterious effect of CV is DCI due to disruption of cerebral blood flow. In normal patients with intact cerebral autoregulation, cerebral blood flow (CBF) remains constant over a range of cerebral perfusion pressures (CPP)[7]. In CV the vessels are unable to dilate, causing poor downstream CBF and ischemia. Additionally, the relationship between CPP and CBF becomes linear so that any change in CPP causes a change in CBF[7]. Lastly, aSAH patients are at risk for autodiuresis, negative nitrogen balance, decreased erythropoiesis, and iatrogenic blood loss, further reducing CPP [8]. These physiological consequences set prevention and treatment goals of maintaining CBF by augmenting CPP through mean arterial pressure (MAP), and correcting the physical CV.

Cerebral vasospasm after aSAH is hypothesized to be the result of both cerebrovascular endothelial and smooth muscle-dependent mechanisms. An upregulation of inflammatory cytokines result in endothelium membrane damage, resulting in endothelial cells detaching from the basal lamina possibly due to degradation of intercellular adhesion molecule-1 (ICAM-1) [9]. Exposed collagen IV of the basal lamina increases binding and aggregation of platelets and neutrophils that could possibly form microthrombi or microemboli. Matrix metalloproteinases (MMPs) have been colocalized to areas of degradation of the basal lamina, which negatively affects the integrity of the blood-brain-barrier [10]. Increased MMP activity has been demonstrated downstream in the setting of oxyhemoglobin. MMP-2 subsequently cleaves the extracellular domain of the heparin-binding epidermal growth factor-like growth factor (HB-EGF), which results in activation of the tyrosine kinase EGF receptor. This activation of the EGF receptor results in endocytosis of the vascular smooth muscle voltage-gated potassium channel. Reduction in potassium efflux from smooth muscle cells results in prolonged depolarization and subsequently contraction and vasoconstriction [11].

Nitric oxide is a vasodilating gas that is produced in endothelial cells by nitric oxide synthase. Vasodilation occurs by nitric oxide activating soluble guanylyl cyclase in vascular smooth muscle cells. Hemoglobin released from erythrocytes during hemolysis after aSAH is capable of scavenging nitric oxide and thus decreasing cerebrovascular vasodilation (reviewed by [12]).

Hypoxia is associated with up-regulation and increased protein expression of a potent vasoconstricting molecule, endothelin-1, in cell culture experiments of isolated rat brain microvessels [13]. These in vitro experiments also demonstrated concomitant increase in hypoxia-inducible factor 1α (HIF-1α) in the first 8 hours after exposure to hypoxic conditions (1% oxygen). A potential mechanism of action by which endothelin-1 mediates vasoconstriction is by increasing calcium influx via transient receptor potential proteins [14]. Clinically, aSAH patients with vasospasm have significantly higher endothelin-1 protein levels in their plasma 8 to 14 days after their initial hemorrhage [15].

2.2. Prevention

Euvolemia—In aSAH, hypovolemia is a risk factor for DCI and increased mortality [16], but a 2004 Cochran Review found, however, that prophylactic hypervolemia adds no benefit to euvolemia, and tended to increase rate of complications (RR 1.8; 95% CI 0.9 to 3.7) [17]. Current consensus guidelines recommend maintaining euvolemia and normal circulating blood volume to prevent DCI [5].

Nimodipine—Nimodipine is an L-type calcium channel blocker and is thought to act on the cerebrovascular smooth muscle to prevent CV, though practically this has not been seen with angiography. Nimodipine is currently the only drug approved by the US Food and Drug Administration (FDA) for improvement of outcomes after SAH (in a review of 16 studies there was a relative risk or 0.67 [95% CI 0.55 to 0.81] [18], and is the first line drug used for the prevention of DCI.

Because of nimodipine's frequent dosing and hypotensive effects, a retrospective study found that noncompliance and dosing changes are frequent [19]. EG-1962 is a sustained-release intraventricular delivery system of nimodipine on poly(DL-lactide-co-glycolide) (PLGA) microparticles. Currently the NEWTON trial (Phase 1/2a multicenter, controlled, open-labeled, randomized, dose escalation study) is underway to find the maximum tolerated dose (MTD) for EG-1962 [6].

Angioplasty—The first use of balloon angioplasty to treat vasospasm after aSAH was demonstrated in 1984 by Zubkov and colleagues. The histopatholigical details underlying the effects of balloon angioplasty have since been elucidated. Animal studies looking at the histological changes after balloon angioplasty have demonstrated durable changes lasting 7 to 56 days after angioplasty [20, 21]. Functional changes in endothelial cells as well as thinning and of the internal elastic lamina were the most consistent histological changes noted. Human autopsy studies yielded similar histological changes of the basal lamina and muscle fibers after balloon angioplasty [22].

Prophylactic balloon angioplasty has not been demonstrated to improve functional outcome, furthermore there is also a risk of rupturing the artery as a result of the procedure [23]. Therefore prophylactic balloon angioplasty after aSAH is not recommended. Despite the use of balloon angioplasty there has been no prospective randomized control trials looking at the role of this intervention after vasospasm has been radiographically confirmed. However, multiple case series have established the utility of balloon angioplasty to ameliorate the effects of cerebral vasospasm after aSAH [24]. Rescue angioplasty, with or without

vasodilator agents, has been recommended if aSAH patients remain symptomatic despite induced hypertension up to SBP 200–220 mmHg [25].

Balloon angioplasty has longer durable effects on vessel diameter compared to intra-arterial infusion of vasodilatory agents. The most catastrophic complication of balloon angioplasty is rupture of the vessel, which has been reported to be as high as 4% [26, 27].

Lumbar drain—The first study to look at the potential benefit of placing lumbar drain (LD) after aSAH was by Klimo and colleagues in 2004 [28]. This retrospective study looked at patients with LDs placed in nontraumatic aSAH patients after clipping of aneurysms and EVD placement. The primary outcomes included clinically evident vasospasm, vasospasm-induced infarction, and Glasgow Outcome Score (GOS). Patients that received LDs in addition to EVD had significantly less clinically evident vasospasm and vasospasm-induced infarction. Furthermore, patients with LDs had significantly better neurologic outcomes with GOS of 5 at a 1 to 3 month follow up [28]. The prospective trial (LUMAS) looked at the effect of LD placement on DCI and functional outcome in patients with aSAH undergoing endovascular securing of the ruptured aneurysm [29]. Primary outcome was DCI defined as a drop in consciousness or new neurological deficit that was not present after securing of the aneurysm. Patients with LDs had significantly less DCI compared to standard of care without LD. However, there was no significant benefit in functional outcome, as assessed by the modified Rankin scale (mRS), at 6 months after hemorrhage when comparing patients with LDs versus standard of care control group.

These two studies have prompted a multicenter, multinational prospective phase 3 trial called EARLYDRAIN. Patients are randomized to LD after securing the aneurysm or to best current treatment without LD placement. The primary outcome is functional neurologic status as assessed by the modified Rankin scale. This study (NCT01258257) has an estimated completion date of August 2016. Based on existing retrospective trials and the only prospective trial to date, there is not convincing data to support the use of LDs for improving clinical outcomes after aSAH [30].

Antiplatelets—Part of the pathophysiology of DCI is due to microthromboembolism [31]. The role of antiplatelet agents improving functional outcome has not yielded definitive data to support their prophylactic use. When comparing 7 randomized clinical trials [32] evaluating the role of antiplatelet agents (acetylsalicyclic acid, OKY-046, dipyridamole, and ticlopidine) after aSAH, there is a non-significant trend toward reduced poor neurologic outcome. Given the lack of robust data to support the use of antiplatelet agents prophylacticaly, as well as trend toward increased intracerebral hemorrhage with antiplatelet agents, there are currently no recommendations for the prophylactic use of antiplatelet agents after aSAH.

2.3. Treatment

Triple-H Therapy—When symptoms of DCI emerge the intuitive urge is to hemodynamically correct the fall in CBF by increasing CPP across the narrowed, high-resistance vessel. The most fundamental, mainstay of treatment is hypertension, hypervolemia, and hemodilution (Triple-H therapy). Triple-H therapy has weak evidence,

and when available studies were reviewed, it was found that it was associated with a reduced risk of symptomatic vasospasm (RR 0.45, 95% confidence interval [CI] 0.32–0.65), but not DI (RR 0.54, 95% CI 0.2–1.49), and the risk of death was higher (RR 0.68, (5% CI 0.53–0.87) [33].

According to review studies, hypertension does seem to be the most useful component of Triple-H [34, 35]. Current recommendation is to allow for hypertension in patients with DCI, unless blood pressure is elevated at baseline or there is elevated cardiac risk [5], and to allow rise to occur in a stepwise manner [36].

There is not a consensus on the first line agent for blood pressure augmentation, but the decision should be based on the individual patients, considering factors such as cardiac output and heart [36]. Phenylephrine, norepinephrine, dobutamine, and milrinone have all been studied, and the Hypertension Induction in the Management of Aneurysmal subarachnoid haemorrhage with secondary IschaemiA (HIMALAIA) trial is underway, which will randomize aSAH patients to either an arm of induced hypertension to a maximum MAP of 130 mmHg or systolic blood pressure of 230 mmHg using norepinephrine, dopamine, phenylephrine, or terlipressine, or to the control arm where patients will not have blood pressure augmentation [37].

When tested head-to-head with euvolemia in randomized control trials, hypervolemia showed increased central venous pressures, but no difference in cerebral blood flow, cerebral blood volume, or in incidence of CV [38, 39], while causingincreased hospital costs and complication rates, especially congestive heart failure [38].

Hemodilution is meant to increase rheology by decreasing blood viscosity. As a result there is an increase in CBF, though impairing oxygen delivery capacity [40]. Due to conflicting data regarding hemodilution and anemia, current guidelines state that hemodilution should not be undertaken except in cases of erythrocythemia [36].

Endovascular Treatment—Practices vary regarding timing of endovascular treatment [41], but is has been shown through a multivariable regression model that a response to hemodynamic manipulation within two hours was independently protective against death (adjusted odds ratio, 0.03; $P < 0.05$) and mRS 4–6 (severe disability to death) (adjusted odds ratio, 0.1; $P < 0.05$) [42]. If a patient does not respond within two hours of conservative management, endovascular therapy should be considered.

Endovascular therapy is divided into 2 strategies: direct intra-arterial (IA) pharmacologic vasodilation and direct balloon angioplasty. Common methods of pharmacologic vasodilation include verapamil (an L-type calcium channel blocker) that has been shown to increase ICP [43] and nicardipine (a dihydropyridine calcium channel blocker), though milrinone has also been studied All three methods can cause hypotension and a fall in CPP and have a short duration of benefit [5].

Other noninvasive IA treatments have been studied. Recently, a small prospective, non-controlled trial, studied administration of continuous nimodipine via microcatheter in the external carotid artery for 9–15 days in patients with severe angiographic vasospasm. The

patients all had angiographic improvement and had good outcomes at 3 months [44]. This might provide a less invasive way of managing CV, but further safety, dosing, and controlled trials are needed.

Fever—Fever in aSAH patients has been associated with worse outcomes [45]. Patients with aSAH often present with fever during the course of their ICU course. In one study 54% of aSAH patients developed fever, which were associated with an increased odds ratio of poor outcomes [46]. Current guidelines recommend treatment of fever in patients with aSAH, but multimodal monitoring has demonstrated that there may be detrimental physiologic effects associated with treating fever. When patients with aSAH were treated for fever with the NSAID diclofenac a significant decrease in mean arterial pressure and cerebral perfusion pressure occurred necessitating use of crystalloids, colloids, or vasopressors. A significant decrease in brain tissue oxygen tension followed dicolfenac administration in these patients. These results demonstrate that treating fevers in aSAH patients may also result in decreases in cerebral perfusion pressure and/or brain hypoxia [47].

Intraventricular Nicardipine—Intraventricular nicardipine has previously been used for patients with CV refractory to standard therapies [48]. Webb et al [49] showed improvement in CV assessed as decreased mean flow velocity by TCD after intraventricular nicardipine. The only study evaluating both changes in CV and functional outcome demonstrated a significant reduction in mean flow velocity as measured by TCD in aSAH patients receiving intraventricular nicardipine compared to controls. No significant difference in functional outcomes, assessed by both mRS and GOS, were detected at 30 and 90 days [50].

Transient increase in ICP has been reported in some of these studies, but when multimodal monitoring is employed to look at various other physiological variables such as lactate to pyruvate ratio, cerebral blood flow, partial pressure of brain oxygen tension, and mean arterial blood pressure, those variables did not change significantly after intraventricular nicardipine injection [51]. It should be noted that these variables were only monitored for 6 hours after intraventricular nicardipine injections, which was given every 8 hours. There are currently no guideline recommendations for use of intraventricular nicardipine injections for CV or medically-refractory CV.

Statins—In addition to reducing cholesterol levels, statins produce anti-inflammatory, anti-vasoconstriction and anti-thombotic effects [52]. Six randomized clinical trials investigating the roll of statins in DCI and functional outcome have been conducted. There is evidence that statins decrease the incidence of DCI, but there is no significant effect of statins on functional [53]. A systematic review of four placebo-controlled clinical trials using statin therapy following aSAH yielded no statistically significant benefit in preventing vasospasm, delayed cerebral ischemia, or poor functional outcome [54]. Therefore, most clinicians will maintain their patient on a statin if they were taking one prior to aSAH, but will not start a statin on a naïve patient if there is no clinical indication to do so.

Cilostazol—Cilostazol is a phophodiesterase 3 inhibitor with vasodilatory and antiplatelet properties. In a multicenter prospective randomized trial, patients that received cilostazol

after aSAH had significantly less angiographic vasospasm as well as delayed cerebral ischemia [55]. This trial and others investigating cilostazol after aSAH have been criticized for the small number of patients enrolled. In a meta-analysis of 4 trials involving cilostazol, significant reduction in symptomatic vasospasm, severe vasospasm, delayed cerebral ischemia and poor outcome were seen in patients receiving cilostazol [56]. The only randomized, double-blind, placebo-controlled trial with cilostazol also demonstrated significant reduction in symptomatic vasospasm and improvement in functional outcomes (Glasgow Outcome Scale) versus controls in aSAH patients [57].

Magnesium—Two potential beneficial effects of magnesium in ameliorating the sequelae after aSAH are due to its antagonism of N-methyl-D-aspartate (NMDA) glutamate receptor and that magnesium functions as a blocker of the NMDA channel [58]. A meta-analysis of 7 randomized trials (involving 2047 patients) did not show a significant improvement in functional outcome in patients receiving magnesium compared to control groups 6 months after aSAH [59]. The use of magnesium is not recommended in preventing CV, DCI and improving functional outcome in patients after aSAH.

3. The Role of Precision Medicine - Biomarkers – Mechanisms, Predictive Capabilities, and Treatment Targets

The pathophysiological basis for CV and DCI following aSAH is complex with a cascade of biochemical events that has yet to be fully delineated or completely understood. A considerable number of biomarkers have been investigated as potential mechanistic mediators, predictors of outcome, and treatment targets. These biomarkers range from genetic code to expressed proteome to metabolomic profiles. In the following sections, we will review recent research regarding genomic, proteomic, and metabolomic biomarkers presumptively linked to aSAH and subsequent CV and DCI. For each biomarker, we will discuss proposed pathophysiological contribution, role as predictive tool, and treatment target candidacy. For reference, these are listed in Table 1. From a Precision Medicine approach, each patient's collective genomic, proteomic, and metabolomic makeup can be used to guide individualized treatment. We refer to this collective information as an omic signature.

3.1. Genomics

Apolipoprotein E (ApoE)—The ApoE gene is located on chromosome 19q13.2 and encodes a 299 amino acid single polypeptide chain comprising the main component of very low-density lipoprotein (VLDL), which is integral to lipid transport and metabolism [60]. The human ApoE gene codes for three common alleles, E2, E3, and E4 [60]. The Apoε4 genotype has long been associated with elevated cardiovascular risk [61], and ApoE has been shown to affect acute and chronic responses to neurologic injury [62]. A meta-analysis reported an association between Apoε4 and poor outcome after aSAH [63], though a subsequent study arrived at conflicting data, suggesting ApoE genotypes were not associated with outcome after aSAH [64]. After finding poorer clinical outcomes (as measured by Glasgow outcome scale and modified Rankin scale) in those with Apoε4 but no difference in mortality or incidence of CV, Gallek et al postulated that the ApoE genotype may influence

recovery from aSAH over the longer term [65]. This would suggest that any detrimental effect on outcome caused by Apoε4 may be a result of mechanisms other than CV and DCI, such as its role in inflammation. This is supported by Lynch et al's findings that the ApoE4 isoform appears to be less effective in down-regulating inflammatory cytokines in both brain and peripheral circulations [66]. Interestingly, mice expressing ApoE4 had greater functional deficit, mortality, cerebral edema, and vasospasm compared to those with ApoE3, and mice treated with intravenous ApoE-derived peptide had decreased mortality, functional deficits, and vasospasm [67]. Lastly, a polymorphism of the ApoE -219T promoter was associated with the development of CV after aSAH [68].

Endothelial Nitric Oxide Synthase (eNOS)—The endothelial nitric oxide synthase gene is located on chromosome 7q35 and plays a role in regulation of nitric oxide, which acts as a potent vasodilator and inhibitor of inflammation, smooth muscle proliferation, and platelet aggregation [69]. Given these properties, NO has long been implicated as having a mechanistic role in the development of CV. Several single nucleotide polymorphisms (SNPs) of the eNOS gene have been identified as potentially affecting risk of CV after aSAH. The eNOS gene intron-4 27-base pair variable number tandem repeat polymorphism (eNOS 27 VNTR), although not associate with CV has been shown to predict susceptibility to intracranial aneurysm rupture [70]. The eNOS gene promoter T-786C SNP does predict susceptibility to CV after aSAH [70–72]. Identification of eNOS T-786C genotype in patients with aSAH may allow for early and more aggressive treatment for these patients who are at higher risk of CV and subsequent DCI. HMG-CoA reductase inhibitors (statins) have been shown to enhance cerebral blood flow through upregulation of the eNOS pathway [73]. Phase 2 randomized trials have suggested that acute treatment with pravastatin after aSAH ameliorated CV, improved cerebral autoregulation, and reduced incidence of CV-related DCI [53]. However, the recent STASH(simvastatin in aneurysmal subarachnoid haemorrhage) trial, which is the largest Phase 3 treatment trial assessing acute statin treatment in aSAH, found no benefit in the use of simvastatin in either short or long-term outcomes [74]. Despite these findings, eNOS remains a promising predictor of angiographic vasospasm risk and potential treatment target for vasospasm prevention.

Haptoglobin—The Hp gene codes for haptoglobin, which is an acute phase reactant responsible for binding extracorpuscular hemoglobin. Clearing free hemoglobin neutralizes the negative effects of free radical production, nitric oxide blockade, and inflammatory upregulation [75, 76]. In aSAH, the extravasation of red blood cells into the subarachnoid space and subsequent hemolysis are felt to contribute to both inflammatory and vasoactive cascades. Given its role in counteracting these cascades, haptoglobin is felt to be critical in combating the development of CV and DCI after aSAH. The Hp gene codes for three distinct phenotypes, including homozygous Hp 1-1, homozygous Hp 2-2, and heterozygous Hp 2-1 [77]. aSAH patients with the Hp 2-2 allele have been shown to have significantly greater risk of angiographical CV and progression to DCI [78]. In mouse models, those with Hp 2-2 alleles were more likely to develop chronic CV and higher levels of inflammatory cells within the subarachnoid space [79]. Patient with Hp 2-2 phenotype were associated with higher rates of CV when compared with Hp 1-1 [80]. Furthermore, Leclerc et al found that patients with the Hp 2-2 phenotype were significantly more likely to have moderate,

severe, or global CV, trended toward poorer outcomes as measured by mRS and GOS, and had increased incidence of mortality [81]. Several novel therapies have been effective in preventing vasospasm in mice with Hp 2-2 phenotype, including glutamate receptor antagonists [82], systemic L-citrulline [83], glutathione peroxidase mimetic [84], and controlled nitric oxide delivery [85]. Human clinical trials addressing targeted treatment of those with Hp 2-2 phenotype with novel therapies are lacking. Haptoglobin appears to have a definite role in both inflammation and vasospasm after aSAH and is primed to be act as both a predictor of outcome and treatment target.

Ryanodine receptor—Ryanodine receptors are a family of Ca^{2+} release channels located at the endoplasmic reticulum [86] that are responsible for regulation of intraluminal calcium ions in smooth muscle cells [87]. Ryanodine receptors appear to be involved in regulation of cerebral artery diameter [88], and, as such, may play a role in the development of CV after aSAH. There are three subtypes of the ryanodine receptor (RyR1, RyR2, RyR3), all of which are found in the smooth muscle of cerebral arteries [89]. The RyR1 gene has been found to have three variants (c.5360C>T, c.6178G>T, and c.7244G>A), with the G/T genotype of RyR1 c.6178G>T having an association with increased risk to develop symptomatic CV after aSAH [89]. Dantrolene, an RyR1 antagonist, has been shown in case reports [90] and small series [91] to be effective in treating CV. A randomised, double-blind, placebo-controlled safety trial suggested that treatment of aSAH with intravenous dantrolene was tolerable and safe, though the trial was not powered to evaluate efficacy [91]. A larger clinical trial is necessary to evaluate efficacy.

Plasminogen Activator Inhibitor-1 (PAI-1)—Plasminogen Activator Inhibitor-1 (PAI-1) is a glycoprotein belonging to the family of serpins or serine protease inhibitors [92]. PAI-1 is the primary endogenous inhibitor of tissue-type plasminogen activator (tPA) and urokinase plasminogen activator (uPA) [92]. Given this role, PAI-1 acts primarily as an antifibrinolytic. Plasma levels of PAI-1 are associated with the 4G/5G promoter polymorphisms in the PAI-1 gene [54], with the 4G allele correlating with higher PAI-1 levels [54]. Presumably, higher levels of PAI-1 in patients with aSAH, are at higher risk of developing thrombosis-related cerebral ischemia. This is supported by Vergouwen et al who reported that aSAH patients with the 4G allele in the PAI-1 promoter gene were at increased risk for DCI and had poorer 3 month Glasgow Outcome Scale (GOS) [54]. However, a similar study found no difference in 1 year GOS after aSAH between 4G/5G SNPs [93]. Three PAI-1 inhibitors (Tiplaxtinin, Diaplasinin, and PAZ-417) are in Phase 1 clinical trials [92], though evidence of efficacy in treatment of aSAH is unavailable.

3.2. Proteomics

Endothelin-1—Endothelin-1 (ET-1) is a 21 amino acid peptide produced by endothelial cells and is one of the most potent endogenous vasoconstrictors [94]. ET-1 binds to smooth muscle cells, stimulating calcium influx and subsequent vasoconstriction [94]. Patients with severe CV or DCI after aSAH have higher serum and CSF levels of ET-1 than healthy patients, and the highest levels of ET-1 coincide with the onset of clinical CV [95]. Furthermore, there is an increase in endothelin receptor expression in cerebral arteries after aSAH [96]. ET-1 appears to be produced by activated CSF mononuclear lymphocytes,

suggesting subarachnoid inflammation holding a key role in the upregulation of ET-1 in aSAH [97]. Endothelin receptor antagonists (ETRA) have been shown in clinical trials and an early meta-analysis to prevent both CV and DI but failed to improve mortality or neurological outcomes [98]. Importantly, ETRAs were found to have significant adverse effects including hypotension and pulmonary complications [99]. The apparent disconnect between preventing CV without improving mortality or neurological outcomes suggests that additional factors such as small vessel vasospasm, cortical spreading depression, medication side effects, concurrent critical illness, and microthrombosis may contribute significantly to clinical outcomes.

Tumor Necrosis Factor-α (TNF-α)—Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine and acute phase reactant capable of inducing fever, apoptosis, and recruitment of inflammatory cells [100]. Cerebrospinal fluid (CSF) levels of TNF-α are elevated after aSAH, and patients with poor outcomes appear to have higher levels than those with good outcomes or no aSAH [100]. aSAH patients who develop CV have markedly higher CSF levels of TNF-α than aSAH patients without CV [101]. In rabbit models, intracisternal administration of SB203580 (a TNF-α inhibitor) reversed CV after aSAH and decreased CSF levels of TNF-α compared to controls [102]. In mice, sequestration of TNF-α with etanercept (a biologic TNF antagonist) or prevention of TNF-α release with TNF-α proteinase inhibitor resulted in reversal of SAH-induced myogenic tone, amelioration of SAH-induced neuronal apoptosis, and improvement of neurobehavioral performance [103]. TNF-α inhibitors have also been reported as decreasing microglial activation in experimental models of ischemic and traumatic brain injury, though human trials are needed.

Soluble Tumor Necrosis Factor Receptor-1 (sTNFR-1)—Soluble tumor necrosis factor receptor-1 (sTNFR-1) is a cleaved portion of the transmembrane tumor necrosis factor receptor that is able to bind and effectively inactivate TNF-α [104]. Patients with aSAH were found to have statistically significant elevations of sTNFR-1 in CSF when compared to patients with non-hemorrhagic hydrocephalus, and this elevation correlated with admission Hunt and Hess grade and neurologic outcome as measured by GOS [105]. In our own prospective study evaluating proteomic biomarkers in CSF of patients with aSAH, we found that mean and maximum CSF levels of sTNFR-1 had statistically significant correlation with clinical outcome, with elevated sTNFR-1 levels correlating with poor outcomes as measured by mRS [106]. Given its inhibitory effect on TNF-α, the elevated levels of sTNFR-1 in aSAH are likely indicative of an inflammatory state and not causative of CV or DCI.

Interleukin-6 (IL-6)—Interleukin-6 (IL-6) is a proinflammatory cytokine produced by mononuclear phagocytes that stimulates growth of mature B cells, promotes synthesis of acute phase reactants including C-reactive protein and fibrinogen, and acts on endothelial cells promoting inflammation and coagulation [107]. In patients with aSAH, those with CV had statistically significant elevation of CSF IL-6 on days 4 and 5, and the increase in IL-6 preceded signs of CV [108]. Skoch et al also found a correlation between IL-6 elevation and DCI at 7 days. Similarly, Hendryk et al found that aSAH patients with elevated IL-6 levels between days 0 and 3 were more likely to later develop CV and DCI [109]. Elevated IL-6

upon admission was more likely in those with poor neurological status and was also shown to predict higher risk of DCI [110]. As mentioned previously, intravenous IL-1ra has been shown to reduce CSF levels of IL-6 in patients after aSAH [111], though this was an observation of a safety trial not powered sufficiently to evaluate efficacy.

Interleukin-1 receptor antagonist (IL-1ra)—Interleukin-1 receptor antagonist (IL-1ra) is an endogenous inhibitor of the proinflammatory effects of the cytokine interleukin-1, which is felt to be a key mediator in ischemicbrain injury induced by stroke and subarachnoid hemorrhage [112]. Interleukin-1 also upregulates expression of interleukin-6 (IL-6), which in turn activates a local inflammatory response [111]. The mean CSF levels of IL-1ra were elevated in aSAH patients with poor clinical condition on admission compared to aSAH patient with good condition, IL-1ra levels increased during episodes of DCI, and levels were significantly elevated during days 4 through 10 in patients with aSAH who eventually had poor outcomes [100]. In a phase II safety trial, intravenous (IV) IL-1ra in aSAH patients resulted in reduction in CSF levels of IL-6 with no adverse of serious events, though this did not reach statistical significance due to not reaching target recruitment [111]. The study was not powered sufficiently to evaluate efficacy or impact on outcome. The safe administration and apparent downregulation of IL-6 by intravenous IL-1ra are promising and necessitate larger clinical trials.

Neurofilament (NF)—Neurofilament (NF) are polypeptides that serve as the major structural components of the neuronal cytoskeleton, with subcomponents including neurofilament light (NfL) chains and neurofilament heavy (NfH) chains. Elevated CSF NfL levels were shown to correlate with National Institute of Health Stroke Scale (NIHSS) and World Federation of Neurological Surgeons (WFNS) grading at 10–14 days after aSAH; furthermore, NfL levels also correlated with 1 year GOS scores [113]. Similarly, elevated NfH levels in CSF of aSAH patients correlated with poor outcome at 3 months as measured by GOS [114]. These findings suggest that NF may serve as a biomarker for extent of brain damage and long-term outcome after aSAH.

Other Protein Biomarkers—Several less established biomarkers for CV, DCI, or outcome prediction in aSAH include matrix metalloproteinase-9 [115], markers of thrombin activity (membrane-bound tissue factor, thrombin-antithrombin III complex, and fibrinopeptide A) [116], monocyte chemoattractant protein-1 [117], E-selectin [118], and markers of diffuse neuronal injury (S100B and NSE).

3.3. Metabolomics

Glutamate (Glu)—Glutamate (Glu) is an amino acid that acts as an excitatory neurotransmitter participating in a spectrum of neurochemical pathways. Glu excitotoxicity is suggested as a mechanism for secondary ischemic brain injury, mediated by excessive calcium influx through Glu-mediated ion channels[119]. CSF levels of Glu are elevated after acute brain injury [120], and Glu is a predictive biomarker for secondary brain injury and ischemia after aSAH [121]. Jung et al demonstrated that CSF Glu concentrations correlated with CV and DCI after aSAH. In a canine model of SAH, simvastatin administration attenuated high Glu concentrations [122]. Rosaglitazone, an anti-hyperglycemic

thiazolidinedione, was shown to lower CSF glutamate levels and reduce mortality, CV, and neurological deficits in an experimental rat model [123]. As discussed above, treatment of haptoglobin 2-2 phenotype mice with a glutamate receptor antagonist resulted in prevention of CV [82].

Histidine (His)—Histidine (His) is an essential amino acid and precursor to histamine with strong free radical scavenging characteristics [124]. These free radical scavenging characteristics are felt to be protective in ischemic tissue. Histidine was found to be elevated after aSAH and correlated with CV [125]. Jung et al suggested that, along with other structural amino acids, the elevation in CSF His after aSAH may reflect progressive cell membrane degradation. In a rabbit model, treatment with intravenous His resulted in reduction of CV [124], attributed to its free radical scavenging properties.

Lactate/Pyruvate—Cerebral microdialysis is a novel method of regional neuromonitoring of cerebral metabolism, especially useful in monitoring of tissue oxygenation such as in DCI after aSAH [126]. Commonly measured metabolites include lactate, pyruvate, glutamate, glycerol, and glucose. Elevation of lactate accompanied by decrease in pyruvate is typically indicative of ischemia, though a lactate to pyruvate ratio (L/P) is a more specific marker of ischemia than either indicator alone [127]. Elevated L/P was found to be predictive of poor outcome after aSAH at 12 months as measured by GOS and mRS [121]. With sampling rates as high as multiple times per hour, cerebral microdialysis has the potential to provide nearly real-time monitoring of cerebral metabolism. It is yet to be seen how this may be fully incorporated into treatment decisions regarding secondary brain injury in aSAH.

4. Expert commentary

Patients suffering from aSAH face both immediate and delayed risks of severe neurologic disability and death. Those who survive the initial hemorrhage and associated abrupt rise in intracranial pressure are at risk for CV and DCI for weeks following aneurysmal rupture. Following early aneurysm securement, the primary tools for preventing CV and DCI include maintaining euvolemia and use of calcium channel antagonists, which have replaced the traditional mantra of triple-H therapy. These current techniques are used in conjunction to maintain cerebral blood flow through regulation of cerebral perfusion pressure. Those who develop CV or DCI despite these treatments may be treated with endovascular pharmacologic or mechanical vasodilatation. Other potential prophylactic and treatment modalities include fever reduction, lumbar drainage, antiplatelet, and statin therapy; though the evidence supporting these interventions is mixed and does not support routine use at this time.

The crux of improving outcomes after aSAH lies in understanding the pathophysiology that leads to CV and DCI. The logical conclusion is that if angiographic vasospasm is prevented, delayed cerebral ischemia will not occur. Unfortunately, growing evidence suggests that preventing CV does not insure prevention of DCI or even improved outcomes. Various mechanisms have been proposed as the key mediators of this disease process, including small vessel vasospasm, spreading cortical depression, diffuse micro-thrombosis, and inflammatory upregulation. The large number of proposed mechanisms is outnumbered by

novel biomarkers being championed as mediators of disease mechanism, signals of disease progression, and predictors of clinical outcome. Although these biomarkers hold tremendous promise, it appears unlikely that any single biomarker will provide sufficient sensitivity or specificity to be used as a meaningful clinical tool. However, these biomarkers could be used in conjunction in an individualized manner to transform the current care model for aSAH.

As a theoretical model, an “omic signature” could incorporate an individual’s genetic, proteomic, and metabolomic phenotype into a powerful predictive tool. Genetic information such as ApoE, eNOS, and haptoglobin genotypes could be obtained upon admission of every aSAH patient. This information could be used to stratify risk of subsequent CV and DCI, provide prognostic information based on published outcome probabilities, and prompt implementation of novel treatments based on individual pathophysiological models. Throughout the course of admission, daily proteomic panels including biomarkers such as endothelin-1, TNF-α, sTNFR-1, and IL-6 could help identify patients trending toward development of CV and DCI and allow for more aggressive prophylactic management. Through the use of multi-modal monitoring, minute-to-minute tracking of brain metabolism could identify the earliest evidence of cerebral ischemia allowing for immediate changes in treatment strategies. As information based on these omic signatures is compiled, phenomic cross-matching can be employed to identify common threads in the pathophysiological development of CV and DCI.

Precision medicine has the potential to revolutionize the prevention and treatment of vasospasm after aneurysmal subarachnoid hemorrhage by transitioning from a reactive treatment model with few therapeutic options to a pre-emptive model based on individualized data. Each level from an individual's genome down to regional brain metabolites can be harnessed to create personalized and targeted interventions.

5. Five-year view

The emergence of individualized genomics due to lower costs, as well as big data analyses of genomic and other omic data, are providing previously undiscovered pathological insights into the disease of aSAH and vasospasm. As more is learned about omic data, individualized therapies and interventions will be made targeting these cellular and molecular pathways. Feasible advancements in the next five years include:

- Decreasing costs of whole exome sequencing, providing insights into genetic risk factors for aSAH, CV, and DCI.
- Big data analyses of omic data incorporating Geographic Information Displays (GIS) to truly understand the interplay among genetic, molecular, and cellular biology processes.
- Based on these big data analyses and omic signatures, further development of tailored therapy for patients, especially those who do not respond to current therapies (e.g. undetectable CSF nimodipine levels).

- Metabolomic and proteomic arrays and other precision medicine laboratory testing will provide risk factor assessment for those at highest risk for vasospasm and DCI and poorer outcome through the use of omic signatures.

6. Key Issues

- Precision Medicine is an emerging paradigm aimed at providing individualized prevention and treatment of diseases through understanding and leveraging patient to patient variation.
- Aneurysmal subarachnoid hemorrhage is a disease which carries tremendous morbidity and mortality.
- A large proportion of this morbidity and mortality is a result of cerebral vasospasm and delayed cerebral ischemia.
- Despite advancements in neurocritical care, cerebral vasospasm and delayed cerebral ischemia remain largely unpredictable and have few prevention or treatment options.
- The primary preventive measure used today is optimization of cerebral blood flow through the use of euvolemia and calcium channel antagonists.
- The primary treatment modalities for patients developing angiographic vasospasm or symptoms of delayed cerebral ischemia include induced hypertension and endovascular interventions such as intra-arterial pharmacologic vasodilatation or direct balloon angioplasty.
- Despite similar phenotypic presentations and the use of standardized preventive and treatment measures, patients with aSAH have significantly heterogeneous outcomes.
- Through the use of genomics, proteomics, and metabolomics - and “omic signatures” - Precision Medicine has the potential to provide more effective preventive measures, biomarkers for earlier detection of CV and DI, and individualized treatment modalities.

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Table 1

Biomarkers, Roles, and Potential Targeted Therapies

A. Biomarker	B. Mechanism	C. Predictor	D. Novel Therapy
ApoE	Lipid metabolism, inflammatory down-regulation	Outcome (GCS, mRS), not mortality/CV/DCI	ApoE-derived peptide (mouse model)
eNOS	Regulation of nitric oxide	CV	Statins, gene therapy
Haptoglobin	Binding extracorpuscular hemoglobin	Outcome (mRS, GOS), CV, DCI	Glutamate receptor antagonists, L-citrulline, glutathione peroxidase mimetic, nitric oxide (mouse models)
Ryanodine receptor	Regulation of intraluminal calcium, arterial diameter	CV	Dantrolene
PAI-1	Antifibrinolytic, tPA inhibitor	DCI	PAI-1 inhibitors
Endothelin-1	Endogenous vasoconstrictor	CV, not outcome	Endothelin receptor antagonists
TNF-α	Inflammatory cytokine	Outcome (GOS), CV	TNF antagonists, TNF proteinase inhibitors
sTNFR-1	TNF-α inhibitor	Outcome (GOS, mRS)	TNF antagonists
Interleukin-6	Inflammatory cytokine	CV, DCI	IL-1ra
IL-1ra	Inhibition of IL-1 and IL-6	Outcome (GOS), DI	IL-1ra
Neurofilament	Neuronal structural component	Outcome (GOS, NIHSS, WFNS)	none
Glutamate	Neuronal excitotoxicity	CV, DCI	Simvastatin, rosaglitazone, gluatmate receptor antagonists
Histidine	Free radical scavenger	CV	Histidine
Lactate/pyruvate	Markers of hypoxia/ischemia	Outcome (GOS, mRS)	none

Table 1. Column A lists the various biomarkers implicated in the pathophysiological cascade responsible for the development of CV and DI after aSAH. Column B describes the specific biochemical mechanism through which each biomarker acts. Column C lists the endpoints each biomarker has been associated with, including clinical outcome, cerebral vasospasm (CV), and delayed cerebral ischemia (DCI). Lastly, Column D lists novel treatments in various stages of development that target the biomarkers and their respective mechanistic pathways.