State of Play Review on Haemorrhagic Stroke

Basic science of intracerebral haemorrhage

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Overview

Intracerebral haemorrhage (ICH) causes brain injury in 3 major ways. Firstly there is the mass effect of the initial bleed, haematoma expansion and oedema formation, which increases intracranial pressure causing distortion of brain structures, and mechanical damage to cells. Secondly, there is neuroinflammation that results in secondary brain damage following ICH, through glial activation, cytokine production and disruption of the blood brain barrier (BBB). Finally, rapid dissolution of clotted blood causes the release of breakdown products, such as haemoglobin, haem and iron, which are toxic, cause oxidative stress through the production of free radicals and brain inflammation.

Mass effect

The mass effect after ICH comes from the initial bleed, haematoma enlargement and later oedema formation. The mass effect also causes mechanical disruption to the structures within the brain usually resulting in midline shift. Mechanical disruption also impacts the individual cells. Physical disruption to the cells of the central nervous system (CNS) has been hypothesised to cause the inappropriate release of intracellular neurotransmitters into the extracellular environment. Glutamate mediated excitotoxicity is already implicated in ischaemic stroke and multiple neurodegenerative diseases. Uncontrolled glutamate release causes excessive NMDA and AMPA receptor activation, increasing intracellular calcium (Ca^{2+}) and sodium (Na^{+}) concentration. This causes mitochondrial dysfunction, lysosome instability and endoplasmic reticulum stress which leads to free radical production and the activation of protein kinases, transcription factors and proteases. These processes cause neuronal death through necrosis, apoptosis and autophagy.

Neuroinflammation

Mechanical cell death and necrosis following ICH causes the release of cellular contents into the extracellular environment. Some of these molecules act as damage associated molecular patterns (DAMP), which induce a sterile inflammatory response. These DAMPs bind to a family of receptors; pattern recognition receptors (PRRs), which includes toll-like receptors (TLR). This causes the initiation of an intracellular signalling cascade leading to activation of Nuclear Factor kappa-B (NF-κB), and mitogen-activated protein kinase (MAPK) pathways. This ultimately results in the transcription of chemokines, cytokines and adhesion molecules, which contribute to the neuroinflammatory response. The pro-inflammatory cytokine interleukin-1 (IL-1) is a particularly important pro-inflammatory mediator and has a naturally occurring endogenous inhibitor, IL-1 receptor antagonist (IL-1Ra). IL-1Ra

has been shown to be neuroprotective in a number of experimental paradigms of brain injury.

Microglia are the first cells to respond to injury within the CNS. They can be activated by red blood cells via CD36, DAMPs released from damaged neurons and also low concentrations of adenosine triphosphate (ATP). They are usually found in a ramified, resting state, upon activation there is retraction of these ramifications giving an amoeboid morphology identical to activated macrophages. Activated microglia are phagocytic and as such aid in clearance of the haematoma, however they also play a major role in the propagation of inflammation. Astrocytes form the neurovascular unit (NVU) with endothelial cells and neurons. Complex communication networks exist within the NVU to modulate cerebral blood flow (CBF) and the BBB. Reactive astrogliosis forms glial scarring which is a mechanism to repair BBB damage and surround and restrict areas of inflammation. However glial scarring can prevent axonal regeneration and reactive astrocytes can also release cytotoxic substances and contribute to neuroinflammation.

Endothelial cells are important in the maintenance of the BBB, disruption of the endothelial cells causes dysregulation of the BBB and promotes oedema formation. In addition the endothelial cells express selectins. Selectins promote neutrophil and leukocyte infiltration, which exacerbates the inflammatory environment. Neutrophils are the first peripheral immune cells to enter the brain after ICH. They release reactive oxygen species (ROS), matrix metalloproteinases (MMPs) and cytokines, which cause disruption to the BBB and neuronal death.

Blood breakdown products

The breakdown products of haemolysis (i.e. haemoglobin, haem and iron) cause neuronal damage through activation of neuroinflammatory pathways, induction of oxidative stress and oedema formation. After haemolysis haem acts on PRRs to stimulate the release of proinflammatory mediators, such as tumour necrosis factor alpha (TNF-α) and IL-1, thereby contributing to the activation of neuroinflammatory pathways. In glial cell culture and organotypic slice cultures haem exposure results in an increase in interleukin-1 alpha (IL-1α) expression. The neurotoxicity of haem is prevented by treatment with IL-1Ra. Haem also causes the up-regulation of adhesion molecules, ICAM-1, VCAM-1 and E-selectin in cultured endothelial cells, leading to increased infiltration of neutrophils and leukocytes.

Research Priorities

- There are clear differences in the rates of progression between animal models and humans in different aspects of the condition, thus more research to understand these translational differences is necessary.
- Lack of key animal models that reflect the human structures / models / pathways.

- Timescales and pathways are different between humans and animals.
- Consequences of initial disruption i.e. the dysregulation of brain barrier and release of inflammatory molecules has been long studied in ischaemic stroke but is less well studied in haemorrhagic stroke – we know the signaling pathways involved but we don't know when they play a role – so a key unknown is when these things happen – the timing of events and spatial location e.g. from hours to days, this should be characterised as well as possible from in vitro and in vivo systems
- A key problem is the lack of good animal models that reflect neural disease in humans
- Stem cell work on the effect of haem products, regenerative mechanisms and repair. Could look at potential mechanism and treatment in neuronal cell culture. There is a strong vascular component which neuroscientists have largely ignored – this is increasingly complex in in vivo systems but could look at on-going vascular pathology in vitro.

Epidemiology

Professor Rustam Al-Shahi Salman

The latest Global Burden of Disease study (GBD) covering the period 1990-2010 included 119 epidemiological studies of stroke (58 from high-income countries and 61 from low-income and middle-income countries).[i] These studies found an increase between 1990-2010 in the absolute number of people who have haemorrhagic stroke annually (47%), and the number with related deaths (20%) and disability adjusted life years (DALYs) lost (14%). Most of the burden of haemorrhagic stroke was in low-income and middle-income countries and incidence is highest in Asians, making these populations a priority for further research into sub-groups at greatest risk and optimal prevention strategies.

A systematic review found that case fatality rates after aneurysmal subarachnoid haemorrhage (aSAH) have decreased by 17% between 1973-2002, especially in Japan where it was 11·8% lower (95% CI 3·8 to 19·9) than it was in Europe, the United States of America (USA), Australia, and New Zealand.[ii] The overall improvement in survival is likely to be due to better healthcare in general as well as specific interventions for intracranial aneurysms (IA) (such as endovascular coiling). Further investigation could reveal whether these regional differences are attributable to methodological, genetic or healthcare differences.

Systematic reviews have found no change in case fatality in population-based studies over several decades from one month (40%) to five years (71%) after ICH,[iii,iv] although improvements have been noted in some individual populations. These observations merit investigation of why improvements have occurred in some

settings and clearly prioritise the search for acute treatments and secondary prevention strategies that may improve patients' chances of survival.

Research Priorities

- Priorities would require a Global perspective due to the nature of regional differences in haemorrhagic stroke – issue for the scope of the Stroke Association funding remit.
- Variation globally on outcomes – due to genetics, treatment following stroke or other factors.
- Outcome has improved over time in specific populations – we should look at those populations to understand outcome improvements better, this will provide insight in order to formulate better treatment pathways.
- To look at improvements over time in specific populations, not necessarily in the UK. Can use London stroke register data to look at different populations – London has a high ethnic and cultural diversity so this data may be a good starting point. Ideally, would want to look outside the UK.
- Higher incidence in the Asian population, but very difficult to recruit this population to a trial.
    - Looking at other databases or using SSNAP data may help.
    - Ben Bray looking at epidemiology in SSNAP and other big databases in Sweden and Finland where the patient numbers are large enough to ask questions
- Treatment of haemorrhagic stroke is changing rapidly in the UK – we also need to look at how process of care affects outcome (Adrian working on this).
- Most of the burden of haemorrhagic stroke exists in Asians and in low-middle income countries, so which are the sub-groups at greatest risk, what are the optimal prevention strategies, and what factors explain global variation in incidence and outcome? (NB does the Stroke Association fund research conducted by UK investigators overseas).
- Outcome after subarachnoid haemorrhage has improved over time, and outcome is much better in some populations, so do healthcare or genetic influences explain these differences in outcome?
- Outcome after intracerebral haemorrhage has not improved overall over several decades, though it has in some populations, so does process of care explain improvements in outcome?

Translational studies in haemorrhagic stroke

Dr Adrian Parry-Jones

Current translational studies in ICH

Translational research aims to overcome 'roadblocks' in the pathway between discoveries in basic science and their implementation in clinical practice, ultimately leading to benefit for patients[1]. The first roadblock (referred to as 'T_1') is concerned

with the “transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans”. The second (‘T_2’) is “the translation of results from clinical studies into everyday clinical practice and health decision making”[2]. Here we describe the current situation for T_1 translational research in ICH and the gaps to be addressed to facilitate the successful development of new treatments for ICH based on laboratory research.

Over 100 putative neuroprotective treatments have been taken to clinical trial in ischaemic stroke without success[3], leading to recommendations in light of the failure to overcome the first translational roadblock in ischaemic stroke research. Far fewer preclinical studies testing novel interventions have been performed in ICH and only a few treatments have progressed to clinical trial, but these recommendations are just as relevant to ICH and should be followed to avoid repeating the same mistakes[4]. Informed by guidelines for clinical trials[5], recommendations have been made for the conduct[6] and reporting[7] of laboratory studies testing new treatments in animal models of stroke. These include key steps to reduce bias, including the use of randomisation, allocation concealment, blinded assessment of outcomes, and *a priori* specification of inclusion and exclusion criteria, and a sample size calculation. As interest in ICH grows and we accrue more published studies of novel interventions in animal models of ICH, it is vital that we synthesise this research scientifically, through systematic review and meta-analysis[8], to avoid redundancy and waste in research[9].

ICH and ischaemic stroke present to clinicians in a similar manner, requiring brain imaging to distinguish between them. Although there is some overlap, the underlying pathophysiology of ICH is fundamentally different from ischaemic stroke. Much of what we know about ICH pathophysiology has come from the study of animal models and the relevance of this to clinical ICH is determined by how well these models replicate the clinical disease. Two rodent models of ICH are widely used and are less frequently employed in studies using larger animals. The autologous blood injection model is characterised by stereotaxic injection of a fixed volume of autologous blood to a chosen location, often the striatum[10]. The collagenase model leads to a gradually expanding volume of endogenous vessel rupture and bleeding, initiated by stereotaxic injection of bacterial collagenase[11]. A model of spontaneous vessel rupture following pharmacologically induced hypertension has also been developed in the mouse[12].

Clinical studies can also reveal much about the pathophysiology of ICH. Post-mortem studies were responsible for many early insights into the pathophysiology of ICH[13] and studies using ‘omics’ approaches on tissue samples collected at the time of neurosurgery can provide a wealth of information about gene expression, protein release and metabolic processes[14]. Advances in magnetic resonance imaging (MRI) allow non-invasive assessment of key structural changes and physiological

processes including vasogenic and cytotoxic oedema, blood-brain barrier integrity[15], CBF, deposition of blood breakdown products and structural integrity of white matter tracts. Imaging of radiolabelled tracers using positron emission tomography (PET) has provided important evidence against the existence of an ischaemic penumbra around intracerebral haematomas, with important implications for the safety of acute blood pressure (BP) lowering therapy after ICH[16].

Through the use of these approaches, an understanding of the processes leading to damage after ICH has arisen and key therapeutic targets identified[17]. The initial bleed leads to immediate, irreversible physical injury but processes in the brain surrounding the haematoma contribute to injury, including the damaging effects of thrombin, haemoglobin and its breakdown products (including iron and haem), and inflammation[17]. Based on preclinical research, several agents are currently being tested in on-going clinical trials. These include the iron chelator deferoxamine[18], the peroxisome proliferator-activated receptor agonist pioglitazone[19], and the pluripotent tetracycline antibiotic minocycline[20]. These trials will be the first to test therapies identified by preclinical ICH research in early phase clinical trials, providing preliminary evidence regarding translational research in ICH. Previous negative trials of other treatments in ICH were undertaken either on the basis of findings in animal models of ischaemic stroke (e.g. NXY-059[21], gavestinel[22]), results from other related clinical conditions (dexamethasone[23], mannitol[24]) or other clinical evidence (Factor VIIa[25]). However, preclinical studies testing dexamethoasone in animal models of ICH over 20 years after early termination of a negative clinical trial (which showed no evidence of benefit and increased infections and diabetic complications), have shown improved histological and functional outcomes[26]. Whilst this provides preliminary evidence of a disparity between the response of animals and humans to the same treatment after ICH, we await the results of on-going studies to provide the first true test of translational research in ICH.

Future **research**

With advances in technology, we are now more able to study ICH in humans than ever before. There is renewed and growing interest in studies collecting post-mortem brain tissue and by using advanced histological and molecular biology techniques, novel insights may be provided that were not previously possible. Trials of minimally invasive surgery and haematoma drainage[27] as well as the use of microdialysis[28] in ICH will allow sampling from within and around the haematoma, allowing direct measurement of key mediators and metabolites. MRI is now widely available and PET imaging is available in selected patients at specialist centres. These techniques allow non-invasive assessment of intracerebral processes *in vivo*, and are likely to be especially useful in assessing smaller ICHs, that rarely lead to early death and thus are largely absent from post-mortem studies. Different radiolabelled PET tracers can be used to probe processes including deposition of amyloid and microglial activation, a key part of the inflammatory response to ICH. Further investment in

these approaches will allow important research questions to be addressed directly in clinical ICH patients, avoiding the translational roadblock altogether.

Where it is not possible or unethical to address research questions in humans, such as in the early testing of novel therapies, animals models will continue to play a critical role. However, there remain a number of significant shortcomings:

Priorities for Research

- Further investment into current approaches such as collecting post-mortem brain tissue, magnetic resonance imaging and PET imaging will allow important research questions to be addressed directly in clinical ICH patients.
- Current animal models lack some of the key features of the clinical disease, including spontaneous vessel rupture leading to large haematomas and early haematoma expansion.
- Although some studies have already recognised the importance of testing treatments in animals representative of typical ICH patients, many studies are conducted exclusively in healthy, young, male rodents lacking any of the co-morbidities common in ICH patients.
- Clinical ICH has clear aetiological subtypes and it is important that this is reflected in animal models. The use of models specifically representative of ICH caused by chronic hypertension, cerebral amyloid angiopathy and vascular malformations would help to understand how aetiology influences response to treatment. These subtypes differ in terms of the underlying vasculopathy and anatomical location of acute haematomas, with implications for the progression of injury, optimal protocols for functional testing (subcortical vs. cortical lesions) and response to treatment.
- There is already evidence that processes progress more quickly in animal models than the clinical disease. For example, cerebral oedema does not peak until 1-2 weeks after onset in clinical ICH, but peaks at day 2 in autologous blood injection in rats. The nature and progression of key pathophysiological processes should be compared between clinical ICH and the animal models that seek to replicate it. We require a better understanding of this if we are to use animal models to guide the therapeutic window of potential therapies when progressing to early phase clinical studies.
- Most animal studies are carried out in isolation at single centres leading to variation in how studies are conducted and a lack of transparency. Preclinical multi-centre trials are being established and investigated for ischaemic stroke studies and if successful, it would be logical to apply the same methodology to preclinical ICH research.
- Research to address these key issues is likely to improve the clinical relevance of research using animal models of ICH, helping to negotiate the first translational roadblock in ICH research.

- It is important to follow the steps from guidance from research for ischaemic stroke as ICH is in its infancy.
- Look to exploit all ways to understand ICH in a clinical setting. Work harder to get more samples and to develop more imaging techniques.
- More models need to be developed for humans as the animal models aren't always directly transferrable, due to differing rates of progression and oedema.
- Need to demonstrate clinically that things are happening with post-mortem tissue – so that we know if animal models are true to develop intervention.

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Aetiology of haemorrhagic stroke

Dr David Werring

Terminology

Haemorrhagic stroke is not a precisely defined term, but is generally considered to include several types of intracranial bleeding (i.e. within the skull), including haemorrhage within and around the brain (e.g. intracerebral, subarachnoid, subdural, extradural haemorrhage). Haemorrhagic stroke may also be used to describe bleeding into an area of infarction. Thus, a more precise definition of the pattern of bleeding, for both clinical and research purposes, is preferred. Here we will consider ICH and aneurysmal aunarachnoid haemorrhage (aSAH), the most commons form of intracranial bleeding, which refer to bleeding into the brain parenchyma (ICH) and into the subarachnoid space (aSAH) respectively.

ICH

Conventionally ICH is classified as 'traumatic' or 'spontaneous' (i.e. 'non-traumatic'). The spontaneous group is further subdivided into 'secondary' (due to identified causes including bleeds into tumours, cavernomas, arterio-venous malformations, CNS infection, cerebral venous sinus thrombosis, bleeding disorders, etc.) or 'primary' if there is no obvious underlying cause. Establishing the type and cause of ICH is critically important in defining the likely prognosis and targeting preventive treatment to reduce the risk of recurrent ICH. The term primary is generally considered to reflect ICH due to cerebral small vessel diseases (SVD), but has been criticised because it does not fully describe any true underlying pathological processes, yet may encourage a spurious diagnostic certainty and failure to pursue further investigations. A discussion of the nature of causation is beyond the scope of this review, but a 'cause' can most simply be defined as a factor affecting the prevalence, likelihood or clinical effect of a disease. For ICH, contributory causes include two main types of SVD processes 1) an arteriolar process often related to aging and other common vascular risk factors (e.g. hypertension and diabetes), characterised pathologically by lipohyalinosis, arteriolosclerosis or fibrinoid necrosis, and typically affecting the small perforating end-arteries of the deep grey nuclei and deep white matter (often termed "hypertensive arteriopathy"); and (2) sporadic CAA, a disease process affecting superficial cortical and leptomeningeal vessels through the deposition of amyloid β. Less commonly, ICH occurs in the context of much rarer genetic SVD or cerebral vasculitides. The challenge clinically is that definitively establishing the presence of the common sporadic SVD types requires obtaining brain tissue with histopathological analysis. The declining rates of post mortems and reducing role of surgery for ICH mean that usually such tissue confirmation is not possible. Thus, criteria based on the brain scan appearances have been developed to make a diagnosis of SVD non-invasively in life. The most widely used diagnostic criteria are termed the "Boston" criteria, which rely on the demonstration of multiple areas of ICH in a strictly lobar distribution (in modern practice generally using blood-

sensitive MRI techniques, e.g. T2*-weighted gradient echo MRI. These criteria have almost 100% specificity, but limited sensitivity for the presence of CAA.

Interaction of SVD and risk factors

Although there is considerable pathological evidence linking these SVD processes to ICH, they do not appear to be in themselves sufficient or necessary causes. Risk factors increasing the likelihood of ICH include increasing age, hypertension, diabetes, lipid profile, smoking, antithrombotic drug use, and heavy alcohol intake. These risk factors may themselves cause or influence the development, progression or clinical expression of SVD. The challenge with many studies of ICH (particularly cross-sectional) is that they are able to show associations, but cannot provide proof (or direction) of causality. Whether an association reflects causation can be considered according to the strength of association; consistency; specificity; dose-response relationship; biological plausibility and consistency with disease natural history.

SVD is highly prevalent in older populations, yet ICH, although an important healthcare challenge, is much less common. Thus, as in other types of stroke, spontaneous ICH is likely to result from interplay between environmental and individual patient (e.g. genetic) factors relating to the expression of SVD. Indeed, recent data suggest that genetic variation plays a significant role in ICH risk and outcome. It was estimated that 44% of ICH risk variance was accounted for by genetic risk factors, with a greater contribution of genetic factors (especially apolipoprotein E [APOE] alleles) to lobar ICH than deep ICH.

One model of ICH aetiology is thus that multiple acute or chronic risk factors (e.g. age, sustained hypertension or short-term BP fluctuations, antithrombotics, serum cholesterol levels or statin use, minor head trauma, etc.) interact with vulnerable damaged small vessels (subject to the influence of genetic or other individual patient factors), which, when a certain threshold is exceeded, rupture to culminate in ICH as represented in figure 1. Indeed, a recent population-based study suggested that ICH may result from short-term increases in BP prior to ICH (over weeks to months), by contrast with ischaemic stroke. Thus consistent, long-term BP control may be important in reducing the risk of ICH.

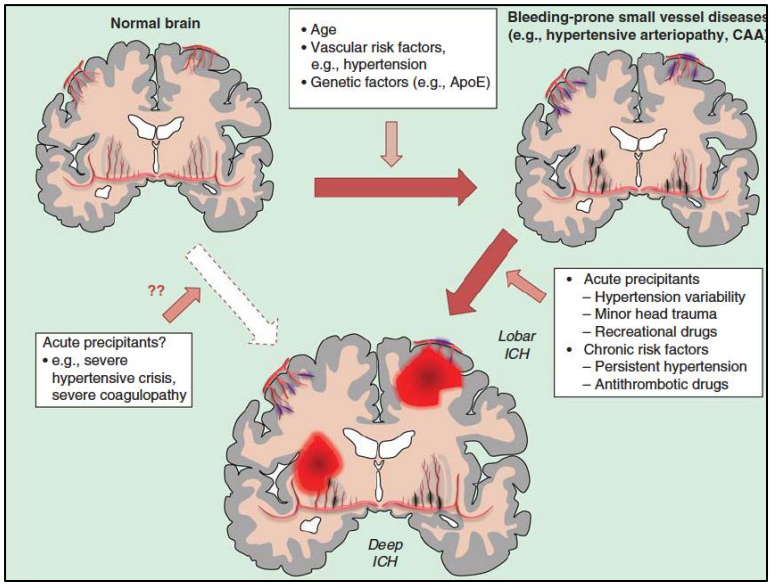

Figure: aetiology of ICH (from Wilson et al, 2014)

Aneurysmal subarachnoid haemorrhage

Due to rupture of an IA, aSAH accounts for about 5% of all strokes in the United Kingdom (UK). Stroke from aSAH is often devastating: half of such patients die within the first month, and of those surviving beyond this, half still require help with daily activities (mobility, dressing, bathing etc.). Because half of the patients are under 60 years old, aSAH causes a huge socio-economic burden. Up to about 6% of the healthy general population (around 3.8 million people in the UK) have an IA). Unruptured IA are increasingly detected by brain imaging. The decision of whether to treat an unruptured IA (by neurosurgical or endovascular treatment) is challenging because only a small minority of IA will rupture, and this risk is currently difficult to predict.

Determining the aetiology of aSAH (and thus IA) faces similar challenges to those in ICH. Like other complex diseases, there is likely to be interplay between genetic susceptibility and environmental risk factors. There is now very strong evidence for a genetic component to IA. There is an increased risk of aSAH in first-degree relatives of those with aSAH (relative risk up to 6.6). A recent comprehensive and systematic meta-analysis on all previously studied single nucleotide polymorphisms (SNPs) (including those identified in recent large Genome-Wide Association Study (GWAS)) associated with IAs, which identified 19 SNPs associated with IA. The genetic variants associated with IA are likely to be biologically relevant as they are involved in vascular endothelial maintenance, integrity of the extracellular cellular matrix (ECM) and inflammation.

IA rupture risk

Known risk factors for rupture include hypertension and smoking, female gender, but, interestingly the strongest factor identified in the most recent individual patient pooled analysis of 8382 participants with IA, apart from aneurysm size, was ethnic

origin, with the highest rupture risk seen in Japanese and Finnish populations (5). It seems highly likely that this large risk effect is due at least partly to genetic factors, necessitating further genetic association studies scanning the entire genome in patients with ruptured and unruptured IA. Microarray-based messenger ribonucleic acid (mRNA) expression profiling allows the study of gene expression, reflecting key functional molecular mechanisms in arterial tissue. Although studies to date are limited, this technique has promise for understanding mechanisms of rupture and IA development in much smaller numbers of individuals.

Research Priorities

- There is a need for detailed clinical and imaging characterisation of patients with ICH, using neuropsychological testing for cognitive function, MRI and other advanced imaging techniques, genetic testing, and circulating biomarkers (e.g. CSF). This will allow the prognosis of different ICH types to be established (e.g. clinic-radiologically defined CAA seems to have a much higher recurrence risk of up to 10% per annum, compared with other types of ICH). This will also allow biomarkers of change over time to be developed to evaluate future treatment interventions aimed at reducing the clinical effects of ICH. Detailed disease characterisation in life ideally needs to be confirmed by histopathological analysis of brain tissue to definitively prove the underlying arterial abnormalities. This requires investment in vascular brain banking and vascular neuropathological expertise.
- Funding is needed for experimental work and early phase clinical trials to begin to translate promising disease-modifying preventive therapies targeted at underlying causes of ICH, e.g. amyloid depleting therapies to specifically target CAA.
- Large scale genetic analysis of well characterized clinical cohorts will allow the identification of new genetic risk variants to shed light on new biological pathways of ICH causation (e.g. genetic risks for CAA).
- Further work is needed to predict the individual risk for developing an IA, and particularly to predict rupture risk to guide treatment. This requires genetic and clinical studies of well-phenotyped cohorts of patients with aSAH and IA, in partnership with large-scale international collaborations.
- More information is needed on underlying mechanisms of disease processes to design therapies to prevent development, progression and rupture of IA. Such insights are likely to come from studies of genetic associations, mRNA expression and circulating biomarkers.
- Terminology is an issue – haemorrhagic is not a good term as some would include infarction.
- There are many different subtypes of haemorrhagic stroke as with ischaemic e.g. primary intracerebral haemorrhage is not a homogeneous entity – different causes within primary group may behave differently.
- There are 2 types of small vessel disease that haemorrhagic stroke is classified into: hypertensive arteriopathy and sporadic cerebral angiopathy.

- There may be very different behaviours in different types of haemorrhage – imaging would be a priority to help us understand this.
    - Aetiology is a more complex question than it seems – interactions with small vessel processes and genetics, environment, patient factors, all on an individual basis.
    - Short-term changes in blood pressure may be crucial (N.B. Peter Rothwell's work), and maybe there are important environmental triggers for changes in blood pressure.
- Detailed characterisation of primary CH – clinical effect and imaging needed to establish distinct subtypes
- Must get treatments that can modify small vessel disease from the experimental bench and into patients.
- Genetics studies to investigate mechanisms and biological pathways of causation
- Need to know more about risk which influence rupture risk in aneurysmal SAH e.g. ethnicity may be a major factor, international large-scale collaboration needed to perform expression studies and look at circulatory biomarkers.
- Should we consider UKBiobank for genetics work – also images of unruptured aneurysms and incident haemorrhage, could do something at the national level, blood samples may be harder to come by? A national SAH biorepository would be a great idea – or even to cover ICH and SAH.

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Acute neurosurgical/neuro Intensive Therapy Unit (ITU) management

Professor Peter Kirkpatrick

Neurovascular and neurointensive care research into intracranial haemorrhage can generally be considered as one. This is a consequnce of affected patients being at the extreme end of the illness spectrum, usually with Coma and/or a neurological deficit requiring a high level of hospital care. Three distinct diagnostic types (in neurosurgery) are recognised on emergency computerised tomography (CT) scan imaging:

1) Subarachnoid haemorrhage (SAH)
2) Intraventricular haemorrhage (IVH)
3) Intracerebral haemorrhage

There is overlap between these entities, with the prime diagnosis being dictated by the dominate CT scan findings

By far the greatest research emphasis has been towards SAH, with a number of high quality randomised controlled trials (RCTs) being published and helping to shape the management of this condition. These notibly include the coiling trial (ISAT) the nimodipine study (BRANT), and recently the statin therapy study (STASH). Many other smaller trials have been conducted to fruition. The majority have been carried out within the UK through the Society of British Neurological Surgeons (SBNS) and the related organisations such as the British Neurovascular Society. Britain holds a particularly strong hand in the research efforts into SAH. However, given the favourable outcome in 80% of SAH patients now recorded in most series (see STASH), the appetite for further pharmaceutical trials into improving outcome by targeting cerebal vasospasm has been diluted and I am not aware of any successor to the STASH trial. Most research in this area will probably focus on technological advances of the coiling devices used.

IVH is under-represented in the research world despite causing a disproportional burden on ITU facilities, and holding considerable morbidity and mortality. There has been a focus into the treatment of neonatal IVH using a tissue plasminogen activator (tPA), but the results are dissapointing. A similar study into adult IVH (Clear-IVH) using tPA has been equivocal. A far more rapid and complete method is required and research into this area is overdue, and in my view this would be a very productive area for research effort, either with novel and rapid acting thrombolytic agent, or microcatheter mechanical means.

Research into ICH has been dominated by trials examining the surgical decisions for evacuation vs conservative treatment; 3 such trials run from Newcastle have all been very dissapointing with neutral results. MISTIE III is a USA run trial exploring the use of tPA infusion into the ICH to facilitate resolution, and is about to start recruitment within Europe. Again UK centres are involved networked through the SBNS.

In many ways research into the IVH problem will mirror those targeting ICH.

None of these research areas dilutes the need to maintain and emphasise on preventative strategies, since this has been the most effective approach especially for ICH.

BP in Haemorrhagic Stroke

Professor Tom Robinson

Background

Stroke is one of the leading causes of death and disability in the developed world [1]; acute ICH being the most lethal and disabling form of stroke [2]. Hypertension is a major modifiable risk factor for stroke, and raised BP is common after acute stroke with at least 75% of patients having a systolic blood pressure (SBP) >130mmHg at hospital admission [3,4]. Increased post-stroke BP is associated with poor prognosis [5,6], and might be caused by raised intracranial pressure [7], increased sympathetic nervous system activity [8], abnormal baroreceptor sensitivity (BRS) [9], haematoma expansion [10], cerebral oedema [11], and a white-coat response [12]. Importantly, recent research shows that SBP is substantially raised compared with usual premorbid levels after ICH, whereas acute-phase SBP after major ischaemic stroke is much closer to the accustomed long-term premorbid level [13]. This difference between the patterns of pre-morbid and immediate post-stroke SBP may provide an explanation for why the risks and benefits of lowering BP acutely after stroke might be expected to differ.

The landmark Intensive BP Reduction in Acute Cerebral Haemorrhage Trial 2 (INTERACT2) did not demonstrate a significant reduction in the rate of the primary outcome of death and severe disability with intensive compared to guideline BP lowering initiated within 6 hours of ICH onset. However, an ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive BP lowering [14], and it is likely that this will impact on forthcoming international and national guidelines for BP management in acute ICH. Furthermore, a post-hoc analysis on INTERACT2 reported that increased SBP BP variability had a significant association with poor outcome; with maximum SBP and standard deviation being the parameters most strongly associated with poor outcome in the hyperacute and acute phases, respectively [15]. The implication is that rapid, smooth and sustained SBP control, particularly by avoiding SBP peaks, may enhance the benefits of early intensive BP lowering. Additional on-going analyses are exploring other mechanisms, including haematoma expansion and perihaematomal oedema, as well as differences between important patient subgroups, for example, those on pre-existing anticoagulant or antithrombotic therapy. Nonetheless, the effectiveness and cost-effectiveness of implementing improved hospital systems to deliver early intensive and sustained BP lowering treatment to improve patient outcome following spontaneous ICH requires further evaluation.

Hypertension is also the most important modifiable risk factor for the prevention of recurrent stroke, with national guidelines recommending a target SBP <130mmHg [16]. The recurrence risk of ICH remains significant, providing an opportunity for secondary prevention; most studies report an overall recurrence rate of 5% per

annum [Charidimou et al, Unpublished data], though this may be substantially higher in lobar ICH with one cohort study reporting a 20% rate over 2 years [17]. Nonetheless, BP lowering may be more effective for preventing deep (hypertension-associated), not lobar (CAA-associated), ICH, and therefore further research studies on secondary prevention of ICH by improved BP control in a well-phenotyped population are essential. The routine use of advanced neuroimaging would also enable the impact of BP control on the natural history of microbleeds to be considered, as well as the development of 'silent' ischaemic lesions. Such studies should additionally explore intensity of BP lowering, single versus combination therapy, role of non-pharmacological therapies, aspects of patient self-management, BP variability as a therapeutic target, as well as the impact of improved long-term BP control on cognitive impairment and dementia following ICH.

Research Priorities

- To assess the effectiveness and cost-effectiveness of implementing improved hospital systems to deliver early intensive and sustained BP lowering treatment to improve outcomes for patients with acute stroke due to spontaneous ICH.
- To assess if an intensive BP lowering strategy reduces the rates of recurrent stroke and cognitive impairment following spontaneous ICH.
- Blood pressure management and implementing the results in ICH is an important area (i.e . Implementation research for blood pressure work that was generated by INTERACT II).
- Implementation research is difficult to do and get funding for, but very important to do – model of care not available to all patients.
- Hypertensive treatment at secondary prevention level as an underlying cause of recurrent haemorrhage – need to better phenotype exactly the type of haemorrhage.
- A well-powered secondary prevention trial in lowering BP would be important but very difficult to actually do, an observational design could be considered.

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Clinical trials in haemorrhagic stroke

Dr Nikki Sprigg

Therapeutic targets

1. Reducing haematoma volume – surgical approaches
2. Preventing haematoma expansion –haemostatic approaches
3. Preventing haematoma expansion –haemodynamic approaches
4. Other approaches–aimed at reducing neuronal injury and oedema desferoxamine, minocycline, cooling

1. Reducing haematoma volume – surgical approaches

Craniotomy -The STITCH 1 and 2 RCTs compared craniotomy with conservative treatment, and failed to show significant benefit for surgery, although there was a non-significant trend to improved outcome in a subgroup of patients.(1, 2).Minimally invasive surgery is the focus of current on-going studies. The series of MISTIE trials have tested stereotactic removal combined with thrombolysis in patients with ICH.(3, 4) MISTIE-III is a phase III, randomised, case-controlled, open-label, 500-subject clinical trial of minimally invasive surgery plus recombinant tissue plasminogen activator (r-tPA) in the treatment of ICH. Another study is on-going in China (SATIH).(5, 6).In patients with IVH, clot lysis is being tested in the series of CLEAR IVH studies.(7) The Clot Lysis Evaluating Accelerated Resolution on IVH III (CLEAR IVH III) is a large RCT investigating the effectiveness of r-tPA in IVH. http://braininjuryoutcomes.com/clear-about

2. Preventing haematoma expansion - Haemostatic approaches

Factor VIIa

Recombinant rFV11a when tested in an early phase 2 trial attenuated haematoma growth (50%) and lowered mortality (18%).(8) However, in the larger phase 3 trial assessing rFV11a involving 816 patients (20 and 80 µg versus placebo)(9) no significant differences in outcome were observed between the three groups. Furthermore, there was a 5% increase in the number of venous and arterial occlusive events in those treated with rFV11a. Two on-going RCT's- STOP-IT and STOPLIGHT.(10, 11) testing rFVIIa are attempting to recruit those at greatest risk of haematoma expansion, by utilising the 'spot sign' on angiography (12).

ICH due to anticoagulation

Haemorrhages related to warfarin are associated with greater mortality.(13, 14) Current treatment varies between centres, and can include fresh frozen plasma (FFP) or prothrombin cell complex concentrate (PCC). The on-going INCH (International normalised ratio Normalisation in Coumadin associated ICH) trial is comparing FFP versus PCC.(15)

ICH in the presence of antiplatelet therapy

A proportion of patients with ICH are taking anti-platelet therapy, and it is know that antiplatelets increase the rate of haematoma expansion and poor outcome. The objective of the Patch study is to investigate whether platelet transfusion within 6 hours after onset of ICH can improve functional outcome by limiting haematoma growth in ICH patients using antiplatelet therapy.
http://www.strokeamc.nl/patch

Tranexamic acid

Tranexamic acid reduces mortality in trauma patients (CRASH-2) with greater efficacy when administered early.(16, 17) Two large phase 3 trials are assessing tranexamic acid in spontaneous ICH. TICH-2 is recruiting patients within 8 hours of onset and STOP AUST is recruiting only "spot sign positive" patients.(18, 19)

3. Preventing haematoma expansion - Haemodynamic agents

Lowering BP may attenuate haematoma expansion. INTERACT-1, and ATACH were phase 2 studies testing the concept of intensive BP lowering therapy to reduce haematoma expansion.(20,21). The phase 3 INTERACT-2 RCT was neutral for its primary outcome, but participants in the intensive arm showed improved functional recovery and quality of life/.(22). Results of the phase 3 ATACH II study are awaited. (23)

4. Other approaches aimed at reducing neuronal injury and oedema– desferoxamine, minocycline

Desferoxamine

Haemoglobin degradation products, in particular iron, have been implicated in secondary neuronal injury following ICH. The iron chelator Deferoxamine Mesylate exerts diverse neuroprotective effects, reduces perihaematoma oedema and neuronal damage, and improves functional recovery after experimental ICH. The investigators of a planned RCT hypothesise that treatment with the iron chelator, Deferoxamine Mesylate, improves the outcome of patients with ICH.
http://clinicaltrials.gov/ct2/show/NCT02175225?term=hemorrhagic+stroke&recr=Open&type=Intr&rank=10

Minocycline

Minocylcine is an antibiotic with neuroprotective effects. The MACH Trial is a pilot study of 400mg minocycline over five days in acute ICH patients. The study will evaluate the safety and efficacy of minocycline in ICH patients
http://clinicaltrials.gov/ct2/show/NCT01805895?term=hemorrhagic+stroke&recr=Open&type=Intr&rank=15

Cooling

Therapeutic hypothermia is being tested as a neuroprotective strategy, and one RCT is using ibuprofen, compared to paracetamol to reduce temperature.
http://clinicaltrials.gov/ct2/show/NCT01530880?term=hemorrhagic+stroke&recr=Open&type=Intr&rank=4

Research Priorities

- Controlling blood pressure (primary and secondary prevention)- could have the biggest impact but there are no trials on this at the moment

- Work looking at anti-inflammatory parading is in the really stages – no large trials as et.
- Simple things e.g. Fluid management, oxygen uptake, process of care, Do Not Resuscitate orders have not been investigated yet.
- Primary prevention
- Efforts so far have focused on preventing Haematoma expansion.
- Neuroprotection studies have so far not proven beneficial, but more, high quality, larger studies are needed.
- Models of care (which differ in the UK compared to Europe) warrant investigation – SSNAP may be a source of data for this.
- Prevention (primary and secondary) with better implementation of BP control guidelines could have a large impact.

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Longer-term outcome in haemorrhagic stroke

Professor Rustam Al-Shahi Salman

A systematic review of longer-term outcome after ICH identified a shortage of population-based studies with follow-up of more than one year describing the risk of not only ICH recurrence but also all other major cardiovascular events.[4] Nine published studies (only one of which was population-based) reported overall annual risks of ICH recurrence varying between 1.3-7.4% over mean durations of follow-up from 1-7 years. Influences on the risk of ICH recurrence were unclear and merit further study. Only four studies reported risks of ischaemic stroke after ICH, which seemed to be as frequent as recurrent ICH: these observations highlight the need for more information about the longer-term risks of all ischaemic and haemorrhagic events, as well as studies of the effects of restarting antiplatelet and anticoagulant drugs after ICH in view of the likely greater overall risk of ischaemic than haemorrhagic events.

The only secondary prevention intervention proven to improve outcome (by reducing the risk of stroke) after ICH is BP reduction with perindopril and indapamide.[v] However, audits show that antihypertensive drug prescription, tolerability, adherence and BP control after ICH could be improved, which could be addressed by further research. Furthermore, in view of the variable influence of statin cholesterol-lowering drugs on outcome after ICH and their known beneficial effects on ischaemic events, whether statins should be resumed after ICH is another secondary prevention dilemma in need of resolution.

As for ICH, a systematic review of longer-term outcome after aSAH found few data on life expectancy after aSAH, and uncertainty about the risks of late recurrent aSAH and other vascular diseases.[vi] As for ICH, restarting (or even initiating) antithrombotic drugs after aSAH may be beneficial, and these approaches merit further study.

Cognitive impairment remains a major influence on poor functional outcome after both ICH and aSAH,[vii] and both a better understanding of its causes as well as interventions to improve it are priorities for future research.[viii]

Intracranial vascular malformations (such as aneurysms, arteriovenous malformations, and cerebral cavernous malformations) are frequent underlying causes of both ICH and aSAH, especially in young people who face longer periods at risk of recurrence than older patients with 'primary' ICH and SAH. Knowledge about the influences on the risk of the occurrence and recurrence of haemorrhagic stroke from these underlying causes over 5 years after diagnosis is emerging.[ix,x] However, further research is needed on much longer term outcomes, how best to convey information about these annual risks to patients, and whether conservative management or treatment are superior in the long-term.[xi,xii,xiii]

Research Priorities

- Knowledge about the influences on the risk of the occurrence and recurrence of haemorrhagic stroke from these underlying causes over 5 years after diagnosis is emerging. However, further research is needed on much longer term outcomes, how best to convey information about these annual risks to patients, and whether conservative management or treatment are superior in the long-term.
- There are currently very few population-based long-term outcome studies for ICH. Average follow-up periods are 1, 2 or 3 years. Need to know more about longer term outcomes, this is a big priority.
    - N.B. Impact of restrictions of grants via the Stroke Association prohibits length of studies to between 3-5 years.
- Very little data to prove if there were any underlying diseases affecting ICH outcome.
- Cognitive impairment – understanding how to improve this and how this works with relation to ICH.
- Interventions to improve outcome: major/simple barriers to interventions
- Questions re statins
- Study the long term effects of treatment versus no treatment – particularly if treatment may cause stroke or death, this is a very difficult decision to make but we need to get better at this and better at counseling patients and their families on the risks - allow better informed decision-making involving patients and families.
- Few long term studies of SAH – ischaemic events are more common than repeat bleed yet physicians stop anti-platelet/anti-coagulant drugs and leave patients open to this risk.
- What is the long-term outcome after intracerebral haemorrhage (i.e. 5 or more years after diagnosis), what is the risk of ischaemic as well as haemorrhagic events, and what influences their occurrence, such as the underlying causes? (N.B. can the Stroke Association fund studies over longer than the usual 3-5 year grant duration to do this?).
- How can antihypertensive drug prescription, tolerability, adherence and blood pressure control after intracerebral haemorrhage improve?

- What is the long-term outcome after subarachnoid haemorrhage (i.e. 5 or more years after diagnosis), especially the risks of late recurrent SAH and other vascular diseases?
- What are the effects of (re)starting antithrombotic drugs and statins after subarachnoid and intracerebral haemorrhage?
- What causes cognitive impairment after subarachnoid and intracerebral haemorrhage and how can it be minimised?
- What are the long-term outcomes for patients with intracranial vascular malformations, is conservative management or treatment superior for unruptured intracranial vascular malformations in the long-term, and how are these risks best conveyed to patients?

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