Aneurysmal Subarachnoid Haemorrhage:

An investigation of the utility of MRI as a non-invasive diagnostic tool and its acceptability as an alternative to lumbar puncture

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I, Joseph Alexander Lansley, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Background

Aneurysmal subarachnoid haemorrhage (SAH) is a potentially devastating but treatable condition, the seriousness of which is not always immediately apparent. An invasive test: the lumbar puncture (LP), is considered a mandatory part of the diagnostic pathway according to guidelines but is frequently omitted in clinical practice.

Aims

1. To establish the extent to which current clinical practice diverges from recommendations.
2. To investigate the beliefs that inform clinician behaviour and establish if the demands required of a diagnostic test for SAH are best achieved by MRI or lumbar puncture.
3. To establish whether MRI has the potential to improve detection of spontaneous SAH compared to CT.

Method

1. The use of LP in cases of suspected SAH was audited at three major teaching hospitals in London.
2. A survey was conducted at major neuroscience centres in London to investigate clinicians' experiences of SAH investigation and their expectations of diagnostic test performance.
3. A prospective imaging study compared the *relative locational sensitivities* of CT and MRI to detect subarachnoid haemorrhage in a group of clinically well patients.

Results

LP was performed in a minority of patients undergoing CT as an investigation for suspected acute SAH (33%). Clinicians demonstrate wide-ranging opinions about the risks and benefits of SAH investigation strategies, with Emergency Medicine clinicians reporting significantly higher risk tolerances compared to Neuroscience clinicians.

Blood-sensitive MRI sequences detected more regions of SAH compared to CT in a cohort of neurologically intact, treatment naïve, spontaneous SAH.

Conclusion

Low adherence to the recommended diagnostic pathway exists in UK practice. This may reflect different risk-tolerances of clinicians and legitimate concerns about the utility of LP. Future guidelines should consider patient and doctor risk-tolerances when making recommendations. MRI has potential value as an alternative non-invasive test and could reduce time, cost and patient discomfort.

IMPACT STATEMENT

Aneurysmal subarachnoid haemorrhage is associated with a high morbidity and mortality when untreated. In an attempt to mitigate the risk of missed diagnosis current guidelines advocate use of an invasive test – the lumbar puncture – in all cases where initial non-invasive imaging is normal. Poor adherence to guidelines has been reported both nationally and internationally.

This thesis contains a detailed review of the scientific basis for the use of lumbar puncture in subarachnoid haemorrhage diagnosis and explores the reasons for poor implementation of recommendations.

Divergence of clinical practice from guidelines may be understood in terms of risk-tolerance. Although risk is a central factor behind clinical decision making, differences in clinician's risk tolerances have been poorly studied in medicine. This thesis indicates that incorporation of risk tolerances into clinical guidelines could help standardise practices and allow clinicians to tailor management strategies and provide individualised patient care.

This thesis also provides evidence that supports the use of MRI in the diagnosis of suspected CT-negative SAH. If used as an alternative diagnostic strategy, MRI could improve the patient experience and the efficiency of the diagnostic pathway – leading to earlier detection of patients with disease and avoiding unnecessary invasive testing of patients with very low risk of disease. For this to be acceptable to clinicians and patients, the LP needs to be appraised in terms of its clinical utility and guidelines need to address the limitations of the LP as a diagnostic test. Further study is also needed to evaluate the clinical utility of MRI in a large cohort of patients with and without SAH. Depending on these findings MRI could prove to be a viable alternative to CT as a first line imaging test for SAH.

Introduction

Patients presenting to hospital with a severe headache of sudden onset pose a difficult diagnostic challenge for the physician. The majority of patients are afflicted by a benign, self-limiting disease, but a small proportion are suffering from a potentially lethal condition and are in need of emergency treatment. Included in this category are patients with spontaneous subarachnoid haemorrhage (SAH) caused by rupture of a cerebral aneurysm. Aneurysmal subarachnoid haemorrhage (aSAH) has an incidence of 6-7 per 100,000 in most populations and costs the National Health Service and estimated £168.2 million annually with a total economic burden estimated at 510 million (Rivero-Arias, Gray et al. 2010).

A reliable diagnosis of aSAH cannot be made on clinical grounds alone (Bø, Davidsen et al. 2008). The ability of currently available diagnostic tools to identify this critical group of patients is imperfect and, to make matters worse, appraisal of the diagnostic tools is itself limited by a number of empirical and theoretical factors.

These issues have made SAH investigation a highly controversial area in medicine and, despite broad consensus expressed in numerous clinical guidelines, there is widespread variation in clinical practice (NCEPOD 2013). The primary aim of this thesis is to demonstrate that non-invasive, advanced MR imaging could be used as an alternative to the current pathway which relies on an invasive test – the lumbar puncture.

To achieve this objective, one might expect no less than a large-scale controlled trial comparing the diagnostic performance of MRI with the existing diagnostic standard. Given the rarity of the disease, this would be no simple undertaking. To date the most comprehensive attempt to evaluate the accuracy of an imaging test (CT) in SAH diagnosis was conducted at a national level, ran over nine years at over 11 tertiary centres, and enrolled 3,132 patients (Perry, Stiell et al. 2011). Even if a comparable study was within the scope of this thesis and MRI was validated as a diagnostic test for SAH, it does not inevitably follow that MRI would be adopted by guidelines or used in clinical practice.

Simple measures of a test's technical performance and diagnostic accuracy alone are insufficient to inform decision makers, physicians, and other users of diagnostic tests. Increasingly, it is necessary to also demonstrate that testing leads to health benefits. "Clinical utility" describes the extent to which diagnostic testing improves health outcomes relative to the current best alternative, which could be some other form of testing or no testing at all (Bossuyt, Reitsma et al. 2012). This is particularly relevant in suspected aneurysmal SAH where the decision to pursue the diagnosis entails ever-more invasive tests (lumbar puncture and catheter angiography) which have low yields and carry some risk of morbidity. Furthermore, these tests may give false positive results which could lead to unnecessary treatments which carry a risk to life.

Therefore, a diagnostic test may have clinical utility by achieving comparable health outcomes in a simpler and safer way. MRI has the potential to provide clinical utility in this manner: as a non-invasive alternative to the lumbar puncture in the diagnosis of aneurysmal SAH diagnosis. In order to evaluate its ability to achieve this, it is necessary to review current clinical practice, appraise the controversies that exist regarding the optimal diagnostic strategy for SAH, and gauge the appetite for an alternative diagnostic strategy. Only with this knowledge can the diagnostic performance of MRI be appraised in terms of clinical utility.

"Subarachnoid Haemorrhage" is a term that indicates the presence of blood in the subarachnoid space. It is not indicative of any specific aetiology or underlying diagnosis. Any disruption of a vessel in, or traversing through, the subarachnoid space can cause SAH. The most common cause is trauma.

Eighty-five percent of non-traumatic SAH cases are caused by rupture of an intracranial aneurysm (van Gijn, Kerr et al. 2007) which accounts for about 5% of all cerebrovascular events in the UK (Stroke Association - www.stroke.org.uk). Ten percent of patients have so called "non-aneurysmal perimesecephalic subarachnoid haemorrhage" (pSAH) which is a benign condition of uncertain aetiology. The remaining 5% of cases are made up of a variety of causes comprehensively described by van Gijn, Kerr et al. (2007) and listed in table 1.

Table 1. Adapted from van Gijn, Kerr et al. (2007)

Inflammatory lesions of cerebral arteries	**Tumours**
Mycotic aneurysms	Pituitary apoplexy
Borreliosis	Cerebral metastases of cardiac myxoma
Behçet's disease	Malignant glioma
Primary angiitis	Acoustic neuroma
Polyarteritis nodosa	Angiolipoma
Churg-Strauss syndrome	Schwannoma of cranial nerve
Wegener's granulomatosis	Cervical meningiomas
	Cervical spinal cord haemangioblastoma
Non-inflammatory lesions of intracerebral vessels	Spinal meningeal carcinomatosis
Perimesencephalic SAH	Melanoma of the cauda equina
Arterial dissection	
Cerebral arteriovenous malformations	**Sickle cell disease, coagulopathies**
Fusiform aneurysms	
Cerebral dural arteriovenous fistulae	**Vascular lesions in the spinal cord**
Intracerebral cavernous angiomas	Saccular aneurysm of spinal artery
Cerebral venous thrombosis	Spinal arteriovenous fistula or malformation
Cerebral amyloid angiopathy	Cavernous angioma at spinal level
Moyamoya disease	
Posterior Reversible Encephalopathy Syndrome	**Drugs**
Reversible Cerebral Vasoconstriction Syndrome	Sympathomimetic drugs, anticoagulant drugs
Hypertension	

Presentation of aneurysmal SAH

The classic case of aneurysmal SAH presents with a distinctive headache of abrupt onset which is typically described as 10/10 in intensity or a “worst ever headache”. The headache is typically associated with neck pain, nausea, vomiting, and sometimes transient loss of consciousness. Physical examination may disclose meningism, ocular haemorrhages and focal or generalised neurological findings (Edlow 2003).

Large or growing, unruptured aneurysms can cause neurological symptoms and signs due to pressure effects on adjacent structures. A classic example is a painful palsy of the third cranial nerve caused by a posterior communicating aneurysm which compresses the third cranial nerve as it traverses between the posterior communicating artery and the rigid dural edge of the tentorial incisura. New or worsening symptoms may indicate aneurysm growth which is associated with rupture. Elsewhere, giant aneurysms may also cause focal neurological symptoms in the manner of any space occupying lesion (Weir 1994).

Natural History of aneurysmal SAH

The outcome of patients with aneurysmal SAH is generally poor. Overall, between 10-15% of patients die at home or during transportation to hospital (Huang and van Gelder 2002) and only 25% of patients can expect to return to a relatively normal life. Half of patients die within one month of the haemorrhage, and of those who survive the first month, half remain dependent for help with activities of daily living (ISWP 2016).

Acute severe headache as a presentation

Headache accounts for 1 – 3 % of Emergency Department (ED) presentations (Morgenstern, Huber et al. 2001, Edlow, Panagos et al. 2008, Knox, Chuni et al. 2012). Sudden onset headaches include a wide spectrum of possible diagnoses, including SAH, benign post-coital headache, exertional headache, intracranial cysts or tumours, intracerebral haemorrhage, hypophyseal apoplexy, sphenoid sinusitis, venous sinus thrombosis, vascular dissection, cerebral vasospasm, and migraine headaches (Carpenter, Hussain et al. 2016). Of the patients presenting to ED with headache, between 1 and 4% have SAH (Edlow and Caplan 2000).

When considering patients with “worst ever” headache as their only symptom the incidence of SAH has been found to be 12% with half of these patients shown to have an aneurysmal cause (Linn, Wijdicks et al. 1994).

Clinical decision rules in SAH

The clinician’s role in managing a patient presenting with headache is to quickly distinguish between primary, non-life-threatening headache syndromes that can be diagnosed and treated without investigation (e.g. migraine), and life-threatening secondary headache syndromes requiring urgent investigation. Of the latter causes, aneurysmal SAH is considered the most important diagnosis not to miss because it is the most common of the secondary syndromes and patients who are not diagnosed at their first point of medical contact are at high risk of re-bleeding which carries a poor prognosis (Davenport 2004).

Like most medical conditions, presentations of SAH vary in severity. Severe cases present with localising neurologic signs or severe alterations of mental status. The decision to pursue investigations is straightforward in such patients, and in those with a typical presentation. Clinical decision making is more difficult in patients who are more mildly affected. Patients who are alert and have no neurological deficit are more likely to be misdiagnosed, paradoxically it is these good grade patients who would benefit most from early identification and treatment (Edlow 2003).

The rate of missed or delayed SAH diagnosis has been reported to vary from 12% to 51% (Adams, Jergenson et al. 1980, Verweij, Wijdicks et al. 1988, Mayer, Awad et al. 1996, Neil-Dwyer and Lang 1997, Kowalski, Claassen et al. 2004). This wide range reflects the inconsistency of study methods and definitions of misdiagnosis and is influenced by risk factors related to the clinical setting (e.g. patient acuity, physician experience and access to diagnostic resources). When considering ED presentations about 1 in 20 SAH patients are missed. Low acuity patients are almost three times more likely to be misdiagnosed compared to more severe presentations (Vermeulen and Schull 2007). This suggests a need for heightened suspicion among patients with minimal clinical findings. Hence, the consensus in SAH investigation is to “err on the side of over-diagnosis rather than under-diagnosis” (Davenport 2004).

Researchers have developed clinical decision rules in an attempt to stratify patients into high and low risk groups based on their clinical presentation. Perry, Stiell et al. (2013) developed the Ottawa SAH Rule which triages patients to further testing if one or more of the following risk factors are present: age >40, neck pain or stiffness, witnessed loss of consciousness, limited neck flexion on examination, onset during exertion, thunderclap character (instantly peaking pain). This rule was devised to achieve 100% sensitivity for detecting SAH. When validated in an independent cohort, this rule did not lead to a reduction in investigations (with CT or LP) compared to current practice (85.7% vs 84.3%). The same group trialled alternative clinical decision rules with less than 100% sensitivity for SAH detection but rejected these on the basis that clinicians would be uncomfortable with a rule that had any inherent risk of misdiagnosis.

Clinical decision rules may lead to standardisation of investigations and decrease missed subarachnoid haemorrhages. However, the cost is a high rate of testing which could lead to more harm than good depending on the natural history of a disease and the potential impact of the investigation and management pathway itself (Hofmann and Welch 2017).

A systematic review and meta-analysis by Hughes, Bond et al. (2018) estimated the global incidence of aneurysmal SAH to be 6.67 per 100,000 persons. Worldwide, almost 500,000 individuals will suffer from aSAH each year, with almost two-thirds in low and middle-income countries. There is a wide variation across WHO regions from 0.71 to 12.38 per 100,000 with Japan and Finland shown to have approximately double the incidence of aneurysmal rupture compared to the typical worldwide population (de Rooij, Linn et al. 2007). The annual incidence of aSAH in the UK is in the order of 8-12/100,000 (NCEPOD 2013).

Tracking the change in incidence of SAH over the last forty years is problematic because changes in the diagnostic paradigm over that period influence the reliability of the diagnosis. Before the widespread availability of CT, SAH was diagnosed on the basis of a history of sudden headache or unconsciousness with presence of blood in the cerebrospinal fluid (demonstrated by lumbar puncture or inferred from neck stiffness) and the absence of prominent focal deficits. These criteria lead to an incorrect diagnosis in 20% of patients with a tendency to over-diagnosis (van Gijn and van Dongen 1980, Linn, Rinkel et al. 1996).

As CT imaging became more widespread, the proportion of imaging diagnoses increased, with a knock-on effect on the apparent incidence of disease. For each percentage point increase in patients investigated with CT scanning, the apparent incidence of SAH decreases by almost 1% (Linn, Rinkel et al. 1996). By the 1990s CT availability and use was ubiquitous in top tier economies so that subsequent trends in incidence of disease reflect the true incidence.

Incidence of stroke has declined by 2% per year over the last two decades which has been attributed to improvements in cardiovascular risk factors (Rothwell, Coull et al. 2004, Pajunen, Paakkonen et al. 2005, Vibo, Korv et al. 2005). Given that smoking, blood pressure and alcohol use have also been identified as risk factors for aneurysm growth and rupture, a reduced incidence of aSAH would also be anticipated. de Rooij, Linn et al. (2007) found a year on year decline in the incidence of SAH of approximately 0.6% after accounting for the influence of region, age, gender and the improved diagnostic reliability that results from

widespread use of CT. The smaller reduction in the incidence of SAH compared with other causes of stroke may in part be explained by the stronger influence of genetic factors in SAH than for stroke in general (Ruigrok, Buskens et al. 2001, de Rooij, Linn et al. 2007).

Aneurysm growth and rupture

Whilst some aneurysms progress to rupture, not all do. An estimated 50 to 80 percent of all aneurysms do not rupture during the course of a person's lifetime which explains how the high prevalence of aneurysms in 2-5% of the population is compatible with such a rare incidence of disease affecting just 6.7 per 100,000 worldwide (Hughes, Bond et al. 2018) .

The processes leading up to aneurysmal SAH can be broken down into distinct steps comprising aneurysm formation, growth, and rupture. Detection and treatment of unruptured aneurysms could lead to poor outcomes and unnecessary patient anxiety if subsequent treatment exposes the patient to risk without benefit. An understanding of the pathological processes leading up to aneurysm rupture is therefore necessary to inform appropriate diagnosis and management.

Risk factors for harbouring CAs and SAH

The contribution and interaction of different factors underlying aneurysm formation, growth and rupture are poorly understood but evidence implicates both genetic and environmental factors (Schievink 1997).

A recent, large meta-analysis that included 1,450 unruptured CAs in 94,912 patients from 21 countries identified autosomal dominant polycystic kidney disease, a positive family history of CA or SAH, female sex, and older age as significant risk factors for harbouring CAs (Vlak, Algra et al. 2011).

Familial Cerebral Aneurysms

Familial clustering of intracranial aneurysms was first described by Chambers, Harper et al. (1954). Several epidemiologic studies have subsequently provided support for a genetic predisposition. Between 7 and 20 percent of patients with

aneurysmal subarachnoid haemorrhage have a first or second degree relative with a confirmed aneurysm (Norrgard, Angquist et al. 1987, Ronkainen, Hernesniemi et al. 1993, Schievink, Schaid et al. 1995, De Braekeleer, Perusse et al. 1996). Cerebral aneurysms are approximately twice as common in those with one affected first-degree relative compared to the general population and twice as common again in those with two affected first-degree relatives. Furthermore, the risk of rupture of familial aneurysms is four times higher than that in the general population (Schievink 1997). Compared with sporadic intracranial aneurysms, familial aneurysms rupture at an earlier age, may be smaller when they rupture, and are more often followed by the formation of a new aneurysm. This observation has informed the practice of screening family members of first degree relatives diagnosed with cerebral aneurysms (Chalouhi, Chitale et al. 2011).

Heritable connective tissue disorders

Aneurysm formation is also observed with a number of heritable diseases of connective tissue and extracellular matrix. Autosomal dominant polycystic kidney disease is the most common heritable disease associated with SAH with 10-13% of affected individuals also shown to harbour cerebral aneurysms. Ehlers-Danlos type IV, fibromuscular dysplasia, and neurofibromatosis type 1, are also heritable disorders implicated with cerebral aneurysms and SAH (Schievink, Michels et al. 1994, Chalouhi, Chitale et al. 2011).

Sex Hormones

Women are at higher risk of aneurysm formation, but female preponderance only becomes evident in the perimenopausal and postmenopausal periods suggesting a protective effect of oestrogen (de Rooij, Linn et al. 2007). An earlier age at menopause is associated with cerebral aneurysms, and hormone replacement therapy protects against aSAH (Mhurchu, Anderson et al. 2001, Ding, Toll et al. 2013). Animal studies also provide evidence for a protective role of oestrogen against the formation and progression of CAs (Jamous, Nagahiro et al. 2005).

Modifiable Risk Factors

Cigarette smoking has been consistently associated with SAH with an estimated risk of SAH approximately three times higher in smokers than non-smokers (Vlak,

Rinkel et al. 2013). The underlying mechanism for this is not known but one hypothesis suggests that decreased effectiveness of α1-antitrypsin in smoking could cause an imbalance of protease and antiprotease activity leading to degradation of connective tissue in the arterial wall. In support of this theory is the observation that genetically determined α1-antitrypsin deficiency is also associated with increased incidence of intracranial aneurysms (Schievink 1997).

Hypertension increases the odds of harbouring a cerebral aneurysm by approximately 3 times compared to the general population. This risk factor seems to have a synergistic effect with smoking with higher risk of aneurysms found in hypertensive smokers than expected based on the individual risk-factors alone: combined odds ratio of 8.3 compared to the expected additive odds ratio of 6 (Vlak, Rinkel et al. 2013).

Risk of Rupture

An accurate prediction of an aneurysm's risk of rupture is essential to allow informed management decisions. Observational studies have consistently implicated size and location of aneurysms as risk factors with higher rates for larger aneurysms, aneurysms of increasing size, and aneurysms arising from the posterior circulation (Wiebers, Whisnant et al. 2003, Morita, Kirino et al. 2012, Murayama, Takao et al. 2016).

The overall annual rupture rates for unruptured intracranial aneurysms (UIAs) followed in observational studies range from 0.54 to 1.4% (Ishibashi, Murayama et al. 2009, Sonobe, Yamazaki et al. 2010, Morita, Kirino et al. 2012, Juvela, Poussa et al. 2013, Murayama, Takao et al. 2016) but there is wide variability. For example, in the International Study of Unruptured Intracranial Aneurysms (ISUIA) the annualised risk of rupture in patients without a history of aSAH was 0.05% but this approaches an 11-fold increase where there is a history of aSAH.

Aneurysm morphology is also implicated in rupture. The presence of irregularities including blebs and "daughter sacs" have been shown to be risk factors according to prospective studies. Other aneurysm indices such as aspect ratio (neck width: dome height) and size ratio (maximum dimension: parent artery

diameter) are implicated but adequately powered prospective studies are lacking (Boulouis, Rodriguez-Regent et al. 2017).

Cigarette smoking is associated both with aneurysm growth and rupture whereas hypertension is believed to predicate aneurysm formation but not rupture. Alcohol consumption, on the other hand, is associated with the rupture of existing aneurysms but not their formation (Chalouhi, Hoh et al. 2013).

Retrospective studies investigating trigger factors for aneurysm rupture have implicated coffee and cola consumption, anger, startling, straining for defecation, sexual intercourse, nose blowing, and vigorous physical exercise (Vlak, Rinkel et al. 2011).

Pathophysiology

Recent evidence from both experimental and human studies indicate a central role of inflammation in cerebral aneurysm formation and rupture. This has been described in detail by Chalouhi, Hoh et al. (2013) and is summarised below. The arterial wall is comprised of intimal, medial and adventitial layers. Smooth muscle cells (SMCs) are mostly concentrated in the media. As well as providing structural integrity to the arterial wall, SMCs are the predominant matrix-synthesizing cells of the vascular wall. Thinning of this layer contributes to aneurysm formation and rupture.

Early in aneurysm formation, SMCs migrate into the intima in response to endothelial injury and proliferate, producing myointimal hyperplasia. Here, SMCs undergo phenotypic modulation changing from a differentiated phenotype (concerned with contraction) to a dedifferentiated phenotype, promoting inflammation and matrix breakdown.

A series of in vitro and in vivo studies by Ali, Starke et al. (2013), found that the phenotypic modulation of SMCs in cerebral aneurysms was induced by tumour necrosis factor-α (TNF-α). Specifically, TNF-α inhibited the contractile phenotype of SMCs and induced proinflammatory /matrix-remodelling genes in SMCs. In a follow-up study, the same group found that phenotypic modulation of SMCs was reversed with a TNF-α inhibitor after aneurysm induction. Collectively, these data

indicate that SMCs promote aneurysm formation, progression and rupture under the influence of inflammatory mediators, particularly TNF-α.

Other cells implicated in aneurysm formation, growth and rupture include macrophages and mast cells which are invariably noted in human aneurysm samples. Tissue-infiltrating macrophages release pro-inflammatory cytokines that lead to recruitment of inflammatory cells and the release of macrophage-derived matrix metalloproteinases (MMPs) that digest arterial wall extracellular matrix. Aoki, Kataoka et al. (2007) demonstrated that the expression of macrophages and macrophage-derived MMPs was closely associated with aneurysm growth, and that selective inhibition of these MMPs blocked aneurysm progression.

Hasan, Chalouhi et al. (2012) found that mast cells were more prominently upregulated in ruptured than in unruptured human CAs. Additionally, mast cell degranulation inhibitors have been found to attenuate the inflammatory reaction in the aneurysm wall and block progression of CAs in mice (Ishibashi, Aoki et al. 2010).

The growing knowledge of the inflammatory processes involved in aneurysmal haemorrhage have opened up the possiblilities for non-invasive therapies to be used in the prevention of aneurysm development, growth and rupture. To date, there is evidence of efficacy for Aspirin in human studies, and many other drugs in animal studies including nuclear factor-κB decoy ODN, statins, Infliximab (TNF-α inhibitor), MMP inhibitor (Tolylsam), MCP-1 inhibitor (7ND), Phosphodiesterase-4 inhibitor (Ibudilast), Cathepsin inhibitor (NC-2300), mast cell degranulation inhibitors (Tranilast, emedastine difumarate), free radical scavenger (Edaravone), and doxycycline (MMPs inhibitor) (Chalouhi, Hoh et al. 2013).

As well as demonstrating potential targets for therapy, knowledge of the inflammatory processes in aneurysm growth and rupture provide the opportuity for targeted diagnostic imaging. Vessel wall imaging and Ferumoxytol-enhanced MRI have shown promise in the identification of active inflammation in aneurysms and have been used to target treatment. Imaging of inflammation in aneurysms could also be used as a surrogate outcome measure for anti-inflammatory

therapies aimed at reducing rupture. If validated, this could serve as a paradigm shift in research as the only currently available outcome assessment – rupture – occurs relatively infrequently requiring large and prolonged studies to derive useful results.

Natural history of aneurysmal SAH

An estimated 12 percent of patients with subarachnoid haemorrhage die before receiving medical attention (Huang and van Gelder 2002). Of those who reach hospital, 2 to 4 percent bleed again within the first 24 hours and approximately 15 to 20 percent bleed a second time within the first two weeks (Brisman, Song et al. 2006). Early treatment to exclude the aneurysm from the circulation therefore reduces the risk of mortality and morbidity related to re-bleeding. In addition, treatment to "secure" the aneurysm, allows for more intensive management of blood-pressure which can help ameliorate the detrimental effects of vasospasm related ischaemia which often complicates SAH.

Overall the case fatality rate is about 50% for aneurysm rupture and an estimated 30% of survivors will have moderate-to-severe disability (Johnston, Selvin et al. 1998).

Treatment

Treatment decisions for ruptured aneurysms are straightforward because there is a dismal prognosis without intervention due to the high risk of re-bleeding. Treatment to secure an aneurysm also allows for aggressive treatment of vasospasm induced ischaemia by HHH-therapy: hypertension, hypervolaemia, and haemo-dilution (Bauer and Rasmussen 2014).

Treatment of unruptured aneurysms is more problematic because of uncertainty about the natural history of the disease and the significant risk inherent in the treatment itself. A number of tools have been developed which harness the data from prospective studies to help inform management decisions. The PHASES study utilises patient and aneurysm specific risk factors (Population, Hypertension, Age, Size of aneurysm, Earlier SAH, Site of aneurysm) to generate a 5-year risk of rupture which can help clinicians and patients making management decisions (Greving, Wermer et al. 2014). Whilst a useful guide to

the risk of rupture, the PHASES score only holds true for the initial 5 years after aneurysm detection because of the limited long-term follow up of data on which it is based. Furthermore, several aneurysm characteristics implicated as risk factors for rupture in case-control studies are not included in the PHASES score. Whilst the PHASES score predicts the risk of rupture, a clinician must also take into account the risk of intervention when recommending repair of an UIA. The Unruptured Intracranial Aneurysm Treatment Score (UIATS) was developed to combine all known risk factors of aneurysm rupture and balance these against risks and benefits of intervention. This serves as a useful guide to decision making with excellent levels of agreement amongst highly informed individuals on UIA management (Etminan, Brown et al. 2015).

There are two treatment options for acutely ruptured cerebral aneurysms in the modern era – the endovascular approach and the neurosurgical approach. The neurosurgical approach was established first by Walter Dandy in 1937 and requires direct access to the aneurysm via a craniotomy (Dandy 1938). Once located, the aneurysm can be excluded from the circulation by the placement of a clip across the aneurysm neck.

Endovascular interventions on the other hand, utilise catheters and wires to access the aneurysm via a puncture of the femoral artery in the groin or radial artery in the wrist. The aneurysm is then accessed by navigating through the vascular tree under fluoroscopic guidance. Once in position, detachable coils are placed within the aneurysm where they promote thrombosis thereby preventing flow and the potential of subsequent rupture. It was only recently, in the 1990s, that detachable coils were approved by the FDA as a treatment for aneurysms. Subsequently, balloons, stents and other devices have been developed allowing treatment of ever-more complex aneurysms. In 2002 the findings of the ISAT trial were published demonstrating the superiority of coiling over clipping in cases amenable to treatment by both techniques (Molyneux, Kerr et al. 2002).

Current guidance is that treatment should be decided by a multidisciplinary team including both experienced cerebrovascular surgeons and endovascular specialists and based on characteristics of the patient and the aneurysm (Connolly, Rabinstein et al. 2012).

Empirical and Theoretical Limitations of aneurysmal SAH diagnosis

A diagnosis of aneurysmal SAH can be confidently made on the basis of a characteristic clinical presentation with imaging demonstrating widespread subarachnoid blood centred around an aneurysm - assuming there has not been enough time to allow redistribution of blood in the subarachnoid space. Occasionally ruptured aneurysms exhibit irregular “nipples” or “blebs” arising from the aneurysm wall which reflect areas of weakness and may indicate the site of rupture and trajectory of haemorrhage. Signs of localised haemorrhage may also be seen directly during the course of neurosurgical aneurysm treatment, confirming an aneurysm as the source of subarachnoid blood. However, not all diagnoses of aneurysmal SAH can be made so definitively.

As described by Kassirer (1989), a degree of diagnostic uncertainty is inescapable in medicine, no matter how much information is gathered. The diagnosis of aSAH is no exception. However, clinical practice and clinical guidelines hold the LP in an exalted status as a gold standard test for SAH diagnosis which may not be justified (Coats and Loffhagen 2006).

It is necessary to examine the qualities and shortcomings of the LP as a diagnostic test for SAH and to acknowledge the theoretical and empirical limitations which undermine our ability to diagnose aneurysmal SAH with certainty. The utility of the LP can then be appraised objectively and the pros and cons of a non-invasive alternative can be assessed fairly.

Lack of definitive diagnostic tests

The inability to visualise an aneurysm on imaging, or detect subarachnoid haemorrhage, may preclude the definitive diagnosis of aneurysmal SAH. Even the detection of an aneurysm in a patient with definite SAH does not necessarily confirm that aneurysm rupture is the cause - especially if the subarachnoid blood is not visible on imaging, or remote from the aneurysm in question.

The confidence in diagnosis of aSAH is strengthened by supportive findings on the one hand and negative results for competing diagnoses on the other. Many of the differential diagnoses for aneurysmal SAH lack confirmatory tests. For example, neither neuroradiological findings or laboratory tests allow a definite

diagnosis of primary angiitis of the CNS (Berlit 2010). Other diseases, such as cerebral amyloid angiopathy, require biopsy for definitive diagnosis, the risks of which may deter conclusive diagnostic efforts (Greenberg and Charidimou 2018). Fortunately, the diagnostic process need not rely on the systematic exclusion of all differential diagnoses because many non-aneurysmal causes are clinically distinguishable. This is not the case with perimesencephalic SAH (pSAH).

Perimesecephalic SAH is a diagnostic entity first described by van Gijn, van Dongen et al. (1985) as a distinct subset of patients with SAH who present in a manner consistent with an aneurysmal bleed but in whom an aneurysm cannot be found. As the name suggests, these patients had a relatively minor blood-load localised to the perimesencephalic cistern and were found to have a benign clinical course which distinguished them from patients with aSAH. The authors postulated a venous or capillary source of bleeding in view of the small volume of blood, its localisation, and benign natural history, however the underlying cause remains unknown.

A diagnosis of pSAH may be tentatively made on the basis of the localisation of blood, but it is considered a diagnosis of exclusion. A comprehensive diagnostic work up is indicated look for an underlying vascular lesion because the disease is otherwise indistinguishable from aSAH (Bashir, Mikkelsen et al. 2018).

Failure of aneurysm detection

Failure to detect an aneurysm could lead to a misclassification of aSAH as pSAH. This could occur when aneurysm size is below the resolution of imaging, or if an aneurysm is temporarily occluded following a bleed. Vasospasm may occur following SAH, if this involves the parent vessel of a ruptured aneurysm the aneurysm may collapse and evade detection. Alternatively, an aneurysm may spontaneously thrombose and escape detection (Inamasu, Nakamura et al. 2003). For these reasons, it is common practice to perform repeat, delayed catheter angiography in known SAH to increase the chance of detecting an occult lesion (Bakker, Groen et al. 2014).

Sensitivity to detect SAH is critical because the costs of missed diagnosis are so high. Clinicians and researchers often indicate that anything less than 100% sensitivity is unacceptable when considering the risk of missed diagnosis of aneurysmal SAH (Perry, Stiell et al. 2013). However, it has been argued that demands for such extremes of safety are unrealistic and unhelpful in medicine (Goodacre 2006).

The notion of 100% sensitivity is implausible in the case of SAH. To achieve perfect sensitivity, a test must detect all clinically significant SAH. “Clinically significant” SAH is difficult to define, but for want of a better criterion, symptomatic SAH could be taken as a useful approximation. The symptoms of SAH are believed to be due to meningeal irritation caused by the presence of blood in the CSF. We can therefore assume that a clinically significant SAH will only occur when blood is present in enough volume to have this effect. If there is a critical volume of haemorrhage that triggers clinical symptoms of SAH, then this threshold volume could dictate the sensitivity requirements of a test for SAH diagnosis. However, blood is cleared from the CSF so the threshold volume of blood required for SAH diagnosis reduces over time. Ultimately, near zero levels of blood will remain in the CSF regardless of the initial volume of haemorrhage. As the level of blood-CSF contamination approximates zero, it becomes theoretically implausible that any test can achieve perfect sensitivity.

In summary, the diagnosis of aSAH is limited by the following factors:

1. It may not be possible to differentiate between aSAH with occult aneurysm vs pSAH
2. It may not be possible to differentiate between aSAH vs a non-aneurysmal cause of SAH with an incidental aneurysm
3. The sensitivity required for SAH detection approximates zero because blood is cleared from the CSF over time
4. Delayed presentation of a benign headache with an incidental aneurysm would be difficult to distinguish from aSAH because SAH becomes undetectable over time

Consequently, the “ground truth” of SAH diagnosis is often uncertain, in both clinical practice and research.

Overcoming the limitations

For the reasons described above there is no reliable gold standard for aneurysmal SAH diagnosis and a degree of uncertainty is inherent in the evaluation of any diagnostic test for SAH. One way to overcome this uncertainty is to artificially induce SAH and measure the performance of tests in the certain knowledge that the condition exists. For ethical reasons this is not possible in human subjects but has been adopted in animal studies (Gustafsson, Rossitti et al. 1999).

An alternative method of controlling the ground-truth against which test performance can be evaluated is to simulate SAH in phantom models (Chakeres and Bryan 1986, Akter, Hirai et al. 2007). Unfortunately, this type of in vitro study is not readily generalisable to real-world clinical cases because it cannot replicate the biological processes that occur in the CSF following haemorrhage.

More commonly SAH research has used the prevailing clinical practice to determine the diagnosis. As a result, research in SAH has included a variety of methods to define SAH which are at times contradictory. In order to make sense of SAH research, it is therefore necessary to be aware of the different methods of SAH diagnoses and how these have developed over time.

Evolution of the diagnostic pathway

Prior to the widespread availability of CT, the diagnosis of SAH was made on the basis of the clinical features of a sudden onset of severe headache, nuchal rigidity and neurological findings (Adams, Jergenson et al. 1980, van Gijn and van Dongen 1980). Lumbar puncture was frequently performed but the method of CSF analysis was inconsistent and had the potential to falsely suggest SAH in patients with an intracerebral hematoma or in patients with a traumatic tap (Adams, Jergenson et al. 1980).

By the mid 1970s it was hoped that newly developed CT imaging would provide a more definitive diagnostic method which could be used in surviving patients (Hatano 1977). Early reports justified these expectations with a number of authors reporting on the diagnostic utility of CT in SAH (Kendall, Lee et al. 1976, Liliequist, Lindqvist et al. 1977, Scotti, Ethier et al. 1977, Modesti and Binet 1978,

Weisberg 1979). CT soon became used routinely as the first line investigation in suspected SAH. Not only did CT allow the detection of SAH, it was able to localise SAH which could indicate the source of bleeding. CT was also able to diagnose alternative causes for the clinical presentation and reveal brain herniation (which precludes safe lumbar puncture) and hydrocephalus which may require neurosurgical intervention.

Despite these significant advances, early reports demonstrated that CT sometimes failed to detect haemorrhage in clinically suspected cases. CT was found to be highly reliable in the early stages of SAH, with >95% of cases demonstrating acute haemorrhage on the first day, but performance tailed off over the next few days and weeks (90.5% after the first day, 73.8% on day 3, 50% after one week) (van Gijn and van Dongen 1982, Adams, Kassell et al. 1983).

Vermeulen, Hasan et al. (1989) asserted the primacy of the LP in the diagnosis of SAH when they showed that xanthochromia had a 100% sensitivity for SAH and that this remained positive 2 weeks after the haemorrhage, long after blood is expected to be undetectable on CT. Over 70% of cases still remained positive for xanthochromia three weeks after the initial haemorrhage. The authors concluded that both a normal CT scan and absence of xanthochromia are required to exclude a ruptured aneurysm (provided the LP is performed between 12 hours and 2 weeks after the ictus).

The recommendations of Vermeulen et al., have led to the widespread dogma that an LP should be performed in cases of suspected SAH when the CT is negative. Three decades later these recommendations have been formalised into guidelines and remain largely unchanged.

Guidelines

A number of guidelines and recommendations have been issued by various authorities. All of which stipulate the need for an LP in suspected SAH if the initial CT is negative (see Table 2).

Table 2. Guidelines for SAH investigation

Guideline/ Authority	Recommendation	Reference
Canadian Neurosurgical Society	The first test for SAH is CT, followed by lumbar puncture when the CT is negative for intracranial bleeding.	(Findlay 1997)
Scottish Intercollegiate Guidelines Network	Patients with thunderclap headache and a normal CT should have a lumbar puncture. Lumbar puncture should be delayed till 12 hours after headache onset.	(SIGN 2008)
Intercollegiate Stroke Working Party	Every patient presenting with sudden severe headache and an altered neurological state should have the possible diagnosis of subarachnoid haemorrhage investigated by: • Immediate CT brain scan • lumbar puncture between 12 hours and 14 days if the CT brain scan is negative and does not show any contraindication • Spectrophotometry of the cerebrospinal fluid for xanthochromia.	(ISWP 2016)
Committee of the SEN Study Group for Cerebrovascular Diseases	The diagnostic study of choice for SAH is brain CT without contrast. If the test is negative and SAH is still suspected, a lumbar puncture should then be performed.	(Vivancos, Gilo et al. 2014)
American Academy of Emergency Medicine Clinical Guidelines Committee	Patients presenting with headache symptoms concerning for SAH can be evaluated safely with NCCT, followed by LP (if CT is negative).	(Meurer, Walsh et al. 2016)
American Heart Association	CT scanning for suspected SAH should be performed (Class I, Level of Evidence B), and lumbar puncture for analysis of CSF is strongly recommended when the CT scan is negative (Class I, Level of Evidence B).	(Connolly, Rabinstein et al. 2012)
European Stroke Organization	Lumbar puncture must be performed in a case of clinically suspected SAH if CT or MRI does not confirm the diagnosis (class II, level B); however, within the first 6–12 h the differentiation between genuine subarachnoidal blood and traumatic admixture of blood may be difficult	(Steiner, Juvela et al. 2013)
Korean Society of Cerebrovascular Surgeons, Society of Korean Endovascular Neurosurgeons, Korean Society of Interventional Neuroradiology, Korean Stroke Society and Korean Academy of Rehabilitation Medicine	CT angiography is recommended to identify the existence of an aneurysm when an SAH is not identified on non-contrast CT, and lumbar puncture is recommended when diagnostic imaging with brain CT and CT angiography is vague	(Cho, Kim et al. 2018)
Japanese Society on Surgery for Cerebral Stroke.	Diagnostic lumbar puncture is highly recommended if the initial CT scan is negative despite the presence of warning signs, or if SAH is clinically strongly suspected despite the delay between onset and presentation	(JSSCS 2012)
College of Emergency Medicine	In patients with suspected SAH and a negative CT scan lumbar puncture is necessary to exclude the diagnosis. Grade B recommendation based on level 2a and 2b studies	(Ferguson 2009)

Challenging the utility of the LP

Failure to do an LP is seen as medicolegally indefensible (Coats and Loffhagen 2006), despite this, real-world practice often fails to comply with the recommendations and the LP is commonly omitted from the diagnostic work-up (O'Neill, McLaggan et al. 2005, Perry, Eagles et al. 2009, Mehrotra, Sookhoo et al. 2010, Muhammed, Teubner et al. 2010, Ditta, Galea et al. 2013, Dobb and

Cooper 2013, Rogers, Furyk et al. 2014). Divergence from clinical guidelines has been attributed to lack of clinician education (Schofield 2004), but others have indicated that alternative diagnostic strategies are informed by clinician preference (Rogers, Furyk et al. 2014) and clinician risk tolerance (Lansley, Selai et al. 2016). Indeed, rather than being due to a lack of judgement, there are a number of practical and pragmatic arguments which challenge the utility of the LP.

Limitations of the evidence

There is no direct evidence to support the use of LP in CT negative SAH. The Vermeulen study used positive CT scans to define SAH and assessed the performance of LP in these patients over the subsequent days and weeks following diagnosis on CT. These findings are not necessarily indicative of how the test performs in patients who present acutely with suspected SAH and a normal CT scan. As Davenport points out, "we want to know the sensitivity and specificity of CSF examination at different time points after headache onset in *CT negative* patients, and these data simply do not exist" (Davenport 2005).

Change in technology

A number of studies have demonstrated modern CT technology has achieved excellent diagnostic performance in the detection of SAH when it is performed acutely. Some researchers have argued that modern generation scanners are more accurate than the early scanners on which diagnostic performance was initially judged (Boesiger and Shiber 2005). CT sensitivities of 100% have been demonstrated by a number of researchers (Cortnum, Sorensen et al. 2010, Perry, Stiell et al. 2011, Backes, Rinkel et al. 2012, Valle Alonso, Fonseca Del Pozo et al. 2018) leading to calls to change the guidelines and forego the LP if patients have been scanned within 6 hours of symptom onset (Edlow and Fisher 2012).

Logistics of the LP

Others have criticised the LP because of practical problems with the test itself. The lumbar puncture is invasive and time consuming. The requirement to perform the procedure 12 hours after symptom onset may require medical admission and associated inconvenience for the patient, financial costs and resource use. It can

be technically difficult in patients due to body habitus, poor patient co-operation and patient anxiety, and can be complicated by post dural puncture headache seen in up to 38% of patients (Kuntz, Kokmen et al. 1992), CSF infection, haematoma, or abscess development (Stewart, Reuben et al. 2014).

Clinical Utility

The appropriateness of the LP in SAH diagnosis has also been challenged on the basis of its clinical utility. Foot and Staib (2001) found that LP frequently did not change the course of clinical management. Others have demonstrated a low yield of aneurysmal SAH diagnosed by LP following negative CT with rates ranging from 0.7 to 4.7% (Foot and Staib 2001, Wood, Dimeski et al. 2005, Brunell, Ridefelt et al. 2013, Gangloff, Nadeau et al. 2015, Hann, Chu et al. 2015, Martin, Teo et al. 2015, Migdal, Wu et al. 2015, Valle Alonso, Fonseca Del Pozo et al. 2018). In addition, LP results are often equivocal in up to 35% of cases (average 17%) (Ditta, Galea et al. 2013, Sayer, Bloom et al. 2015, Valle Alonso, Fonseca Del Pozo et al. 2018).

Coats and Loffhagen (2006) applied a Bayesian statistical approach to the problem of SAH diagnosis and demonstrated how the number of LPs required to detect each SAH increases as pre-test probability decreases. Using estimates of pre-test probability and CT sensitivity derived from the literature they showed that 1,000 patients would have to undergo an LP to find one patient with SAH.[†]

The authors suggest that clinicians would be happy to undertake a large number of LPs in order to detect one SAH because they perceive the benefits of correct identification of SAH very large and the negative effects of LP very small. However, they suggest that the law of diminishing returns must come into effect at some point, so that “the accumulated negative effects (cost) of the increasing number of LPs outweighs the benefit of detecting one SAH”. They highlight the lack of research defining this cut-off point or addressing this question from the patient’s viewpoint.

[†] Estimates made on the assumption that CT is done less than 12 h from the onset of headache in a patient with a pre-test probability of 5%.

Coats and Loffhagen's assessment is based on the notion that the LP correctly identifies occult aneurysmal SAHs and that the negative effects are those of patient discomfort and inconvenience. However, their interpretation should also address another significant shortcoming of the LP – its imperfect specificity for aneurysmal SAH, and frequency of equivocal results. As a reference standard, the LP is less than golden. Results classified as false negatives according to the LP as a reference standard may in fact represent false-positive LPs – a factor that is crucial to consider when designing a study to evaluate a new diagnostic test in SAH.

CSF based diagnosis of SAH - Theory

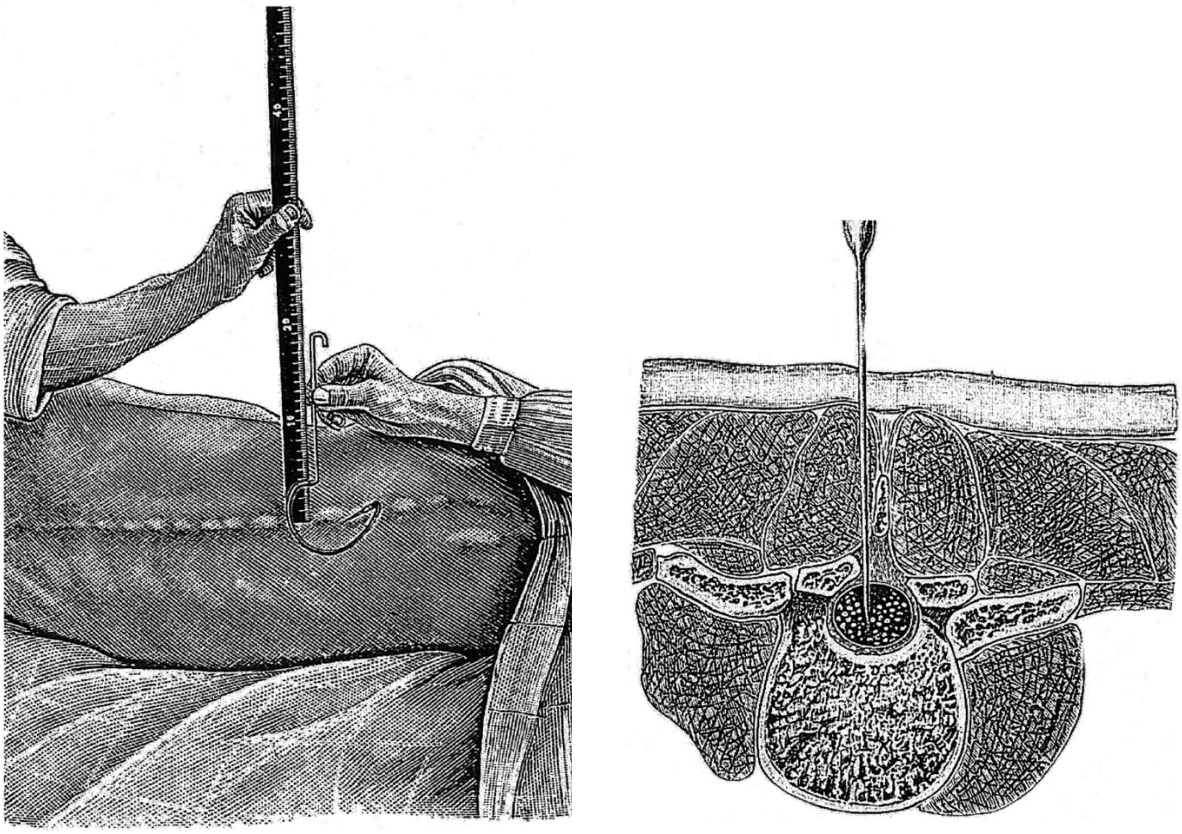
Guidelines recommending the use of "LP" in SAH diagnosis rarely specify a particular method of CSF analysis. However, the evidence base on which current practice is founded incorporates a range of different diagnostic standards which vary in sensitivity and specificity and involve a range of logistical demands which may preclude their widespread use.

A detailed understanding of CSF analysis is required so that the test's diagnostic performance can be appraised appropriately – with reference to a particular method of analysis and interpretation rather than the vague notion of a "positive LP" which is prevalent in the clinical and research literature. Only then is it possible to stipulate the requirements that should be demanded of an alternative test.

Die Lumbalpunktion (Lumbar Puncture)

Wynter (1891) first conceived of therapeutic CSF drainage at the lumbar level but it is Heinrich Ireneo Quincke who is credited with the development of the lumbar puncture as a simpler, less invasive technique. Figure 1 is an original illustration of the technique and is still easily recognisable in routine clinical practice today, over a century later (Quincke 1891). Quincke is also credited to be the first to examine in detail the normal constituents of CSF (Zambito Marsala, Gioulis et al. 2015) meaning that the diagnosis of SAH can be traced as far back as his work in the late 19th century.

Figure 1. Original illustration of Lumbar Puncture and LP manometry (Quincke,1891)



The purpose of performing an LP in suspected SAH is to allow the visualisation of blood in a sample of CSF taken directly from the subarachnoid space. Red blood cells (RBCs) are not a normal constituent of CSF and can be easily detected with the use of a microscope.

The presence of RBCs is sufficient for some to infer SAH (MacDonald and Mendelow 1988, Gerber, Crawford et al. 1998), but in theory RBCs may appear in a CSF sample due to bleeding caused by the lumbar puncture itself. The so called “traumatic tap” may occur in as many as 10-20% of cases (Eskey and Ogilvy 2001). Some authors have argued that the risk of an “ultra-early” re-bleed justifies the use of RBCs detection to define SAH on the basis that it speeds up neurosurgical investigation and management (Gerber, Crawford et al. 1998, Edlow and Caplan 2000), however most clinicians consider the inability to distinguish between a traumatic tap and genuine SAH as a prohibitive shortcoming of this method.

Some clinicians have attempted to distinguish between a traumatic tap and genuine SAH by the “three tube method” whereby CSF is collected in three test tubes with red cells counted in each tube. A falling red cell count in consecutive samples has been taken to indicate a traumatic tap. However, whilst a falling red cell count occurs more often in traumatic punctures, it can occur in patients with a genuine SAH. Moreover, a constant number of red blood cells can be seen in successive samples following a traumatic tap, making the method unreliable (Buruma, Janson et al. 1981). Even if this method could distinguish between a traumatic tap and genuine SAH, it would be falsely reassuring when a traumatic tap occurred in a case of genuine SAH. Consequently, on a case-by-case basis, the “three tube method” does not allow a firm diagnosis of SAH to be made (Vermeulen 1990).

Red blood cells change their morphology when exposed to CSF and appear crenated (Matthews and Frommeyer 1955). Crenation has therefore been proposed as a means to distinguish between traumatic and true haemorrhage. However, crenation of red cells occurs very soon after they enter CSF and can also be seen in traumatic taps (Vermeulen 1990). Cytological assessment of CSF may reveal the presence of cells that digest RBCs (erythrophages) which indicate true intracranial haemorrhage. However, erythrophage appearance is delayed and inconsistent meaning that negative cytology cannot exclude SAH in any given individual (Buruma, Janson et al. 1981). Red blood cells break down rapidly in CSF, so it has also been argued that their absence may not be taken as sufficient evidence to exclude SAH - depending on the timing of the examination (Shah 2002).

For these reasons, it is common practice to spin-down the CSF sample in a centrifuge so that the supernatant can be inspected, free of cellular contaminants, for the presence of pigments released into the CSF following red blood cell lysis. In 1902 Milian and Chiray proposed the term "xanthochromia" to describe the yellow discolouration of the cerebrospinal fluid supernatant following haemorrhage. Xanthochromia is generally held to be the only reliable diagnostic criterion implicating SAH. However, there is no universally accepted definition of xanthochromia which undermines the validity of its use as a reference standard.

Xanthochromia definition and assessment

Barrows, Hunter et al. (1955) identified the pigments responsible for xantochromic discolouration to be oxyhaemoglobin, bilirubin and methaemaglobin. In their seminal work, they utilised the technique of spectrophotometry to “shine a light” on the presence and disappearance of these components in the CSF following haemorrhage. They also identified other disease processes which impart these metabolites into the CSF and were the first to demonstrate that bilirubin formation did not occur in vitro. These observations underpin the methodological requirements necessary to differentiate a traumatic tap from genuine SAH.

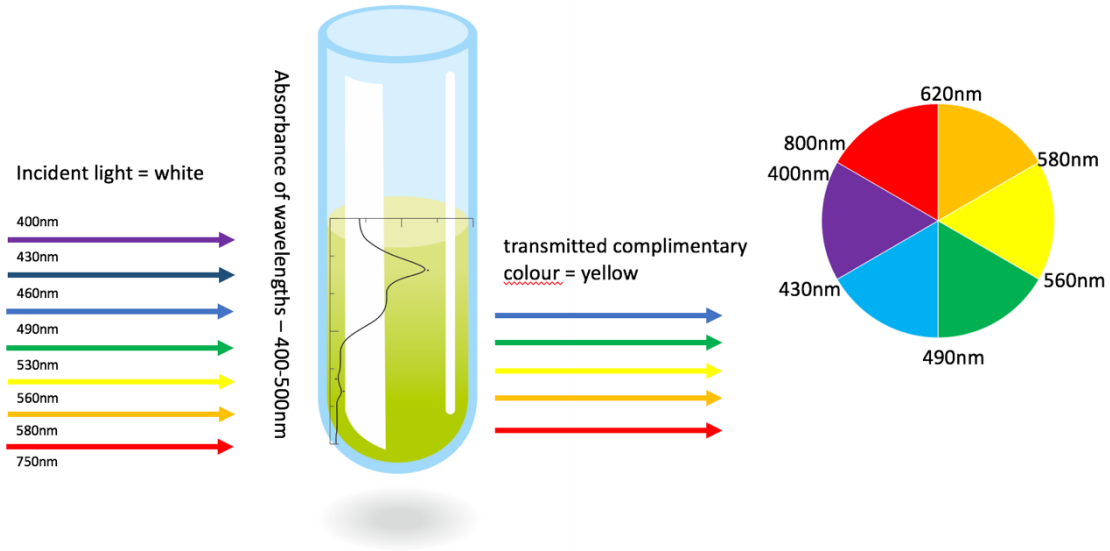
Spectrophotometry

A detailed description of spectrophotometry in SAH can be found elsewhere (Cruickshank, Auld et al. 2008) but a few basic principles need to be understood to appraise current practice, guidelines, previous research, and to appreciate the empirical limitations inherent in its use as a diagnostic test for SAH.

Chemical compounds have characteristic colours in solution which are determined by their absorbance of light of a particular wavelength. Absorbance of the full spectrum of visible light gives a substance a black colour. In its normal physiological state CSF absorbs no visible light, hence it appears colourless.

Pairs of complimentary colours absorb all the wavelengths in the visible spectrum of light. Together, complimentary colours are opposing and strongly contrasting pairings as illustrated by the colour wheel (see figure 2). Absorbance of a specific range of wavelengths of visible light will give a substance a hue determined by the complimentary colour. The yellow discolouration of CSF (xanthochromia) occurs because pigments in the CSF absorb light in the violet range of the spectrum (400 – 500 nm). The corresponding complementary colour is yellow, hence xanthochromia.

Figure 2. Optical absorbance of pigments responsible for xanthochromia



Substances that absorb wavelengths in the visible spectrum of light have a hue determined by the complementary colour of the absorbed light. In the case of xanthochromia, light in the violet spectrum (400-500 nm) is absorbed most by oxyhaemoglobin and bilirubin. As shown in the colour wheel above, the resulting complimentary colour is yellow, hence the visible yellow discolouration of CSF.

It is important to note that different chemical substances may have identical spectral characteristics in a particular region of the visible spectrum. Conversely, the same chemical molecule may show a variety of spectral absorption curves, depending upon the solvent in which it is placed. For this reason, Burrows et al. note that "one should refer to pigments in the cerebrospinal fluid as having the *absorption spectra* of oxyhaemoglobin, bilirubin or methaemoglobin. It must not be inferred from spectrophotometric analysis alone that these pigments are chemically identified".

Cognisant of this limitation, Barrows et al. identified the xanthochromic pigments chemically in their experiments. Using spectrophotometry, they described the characteristic absorption spectra of different pigment types, mixtures, and quantities that arose following the lysis and metabolism of RBCs in the CSF of patients with clinically diagnosed SAH.

CSF pigmentation following haemorrhage

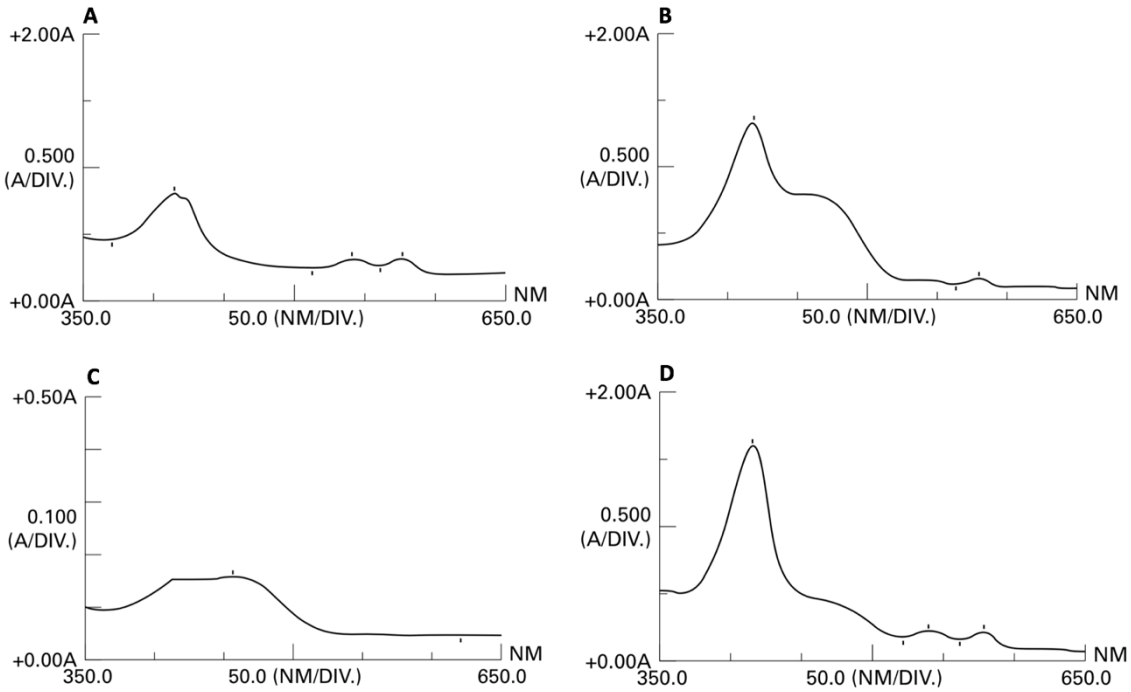
The first pigment to appear in CSF following haemorrhage is oxyhaemoglobin which is liberated following red blood cell lysis just hours after SAH haemorrhage. (figure 3 illustrates the characteristic absorption spectrum). Oxyhaemoglobin

appears orange / orange-yellow on visual inspection due to predominant absorbance at 410 – 418nm. This pigment rapidly increases in vivo to become maximal in the first few days after SAH. If no further bleeding occurs, oxyhaemoglobin gradually diminishes over a seven to nine-day period.

The second pigment to appear in SAH is *bilirubin* the iron-free derivative of haemoglobin. On spectrophotometry bilirubin appears as either a broad peak in the range 450 – 460 nm or a shoulder adjacent to an oxyhaemoglobin peak (if present) and appears canary yellow. Barrows et al. found this to develop over 2 - 3 days and increase as oxyhaemoglobin decreases, persisting for up to 3 weeks depending on the amount formed.

Methaemoglobin, the ferric form of haemoglobin, appears brown and if present, manifests as a broad peak occurring between 403 and 410 nm. Methaemoglobin may form spontaneously from oxyhaemoglobin in vitro but at a slow rate and as such should not normally be found in significant quantities during normal sample processing. Barrows et al., found that methaemoglobin was not ordinarily formed in the subarachnoid space and that its appearance required a special set of conditions in which red blood cells undergo degradation in an enclosed space (such as in subdural haematoma, loculated spinal fluid, cyst fluid or intracerebral haematoma). They suggested that this encapsulation may be required to impede the normal in vivo conversion of oxyhaemoglobin to bilirubin and thereby allow its formation.

Figure 3. characteristic absorbance curves caused by different pigment mixtures



Spectrophotometric scans showing absorbance profiles of blood pigments: (A) oxyhaemoglobin alone; absorption peak at 414 nm, (B and D) oxyhaemoglobin peak with bilirubin shoulder on downslope at 450–460 nm, and (C) bilirubin alone exhibiting a broad peak with maximum absorbance at wavelength of 453 nm. Reproduced from (Cruickshank 2001)

Visual Inspection vs Photospectrometry

In the course of their experiments Barrows et al., were impressed by "the sensitivity of the normal human retina in recognizing the colour changes in spinal fluids". As a screening test for xanthochromia, they recommended comparison of the specimen "by naked eye with clear tap water in tubes of exactly the same size and against a white background". This practice became widely adopted, but instead of being used as a screening test prior to confirmatory spectrophotometry, visual inspection has become established in some centres as a substitute for spectrophotometry (Edlow 2002).

Visual assessment has also been shown to be a relatively insensitive method compared to spectrophotometry. Sidman, Spitalnic et al. (2005) found that visual assessment of xanthochromia achieved a sensitivity of up to 55%. Hence, when used as diagnostic criteria this method can result in false negative results.

Furthermore, visual identification of xanthochromia does not differentiate between bilirubin, which is only formed following in vivo haemorrhage, and

oxyhaemoglobin, which may be produced by a traumatic tap (Buruma, Janson et al. 1981, Shah 2002, Graves and Sidman 2004). Therefore, use of this method as a diagnostic criterion may result in both false positive and false negative results.

Spectrophotometry interpretation

Most authorities on SAH diagnosis hold the view that the utility of the LP is undermined if a traumatic tap cannot be distinguished from a genuine SAH. Xanthochromic CSF supernatant was initially thought to allow this distinction; however, it has since been established that xanthochromia can be caused by the in vitro formation of oxyhaemoglobin following a traumatic tap (Buruma, Janson et al. 1981, Graves and Sidman 2004). The key to making a specific diagnosis therefore relies on spectrophotometric assessment of CSF for bilirubin which is the only detectable pigment formed purely in vivo following SAH. Unfortunately, bilirubin detection is problematic for a number of reasons.

In pigment mixtures highly diluted by CSF, sharp peaks of absorption only occur for pigments with very narrow absorption bands. Oxyhaemoglobin has a very narrow absorption band and is readily apparent in dilute solutions whereas bilirubin, which has a broad absorption band, can easily be obscured. Consequently, if bilirubin detection is required to confirm in vivo haemorrhage, then contamination of a CSF sample with blood introduced at the time of LP can produce enough oxyhaemoglobin to mask a positive result.

Elevated CSF protein can lead to false positive findings because conjugated bilirubin may accompany the protein into the CSF where it may be detected and incorrectly attributed to SAH (Cruickshank, Auld et al. 2008). False positive results may also occur when bilirubin enters the CSF due to elevated serum levels (Griffiths, Ford et al. 2009).

False negative or indeterminate results are also possible if bilirubin (a photosensitive product) is degraded by exposure to light (Foroughi, Parikh et al. 2010). To avoid this, the sample should be protected from light and promptly analysed.

The UK NEQAS criteria outlines standards for specimen handling, analysis, reporting and interpretation and accounts for the possible confounding factors described above. These guidelines outline how bilirubin absorbance levels should be adjusted in the case of raised serum bilirubin levels, ensuring that specificity is retained at the expense of sensitivity. In cases where oxyhaemoglobin is elevated, such that it may obscure bilirubin detection, they recommend an equivocal interpretation: “SAH is not excluded” (Cruickshank, Auld et al. 2008).

CSF based diagnosis of SAH in practice

As demonstrated above there is no universally accepted, standardised method of CSF interpretation and the evidence base on which the use of the LP has been established utilises differing criteria resulting in different levels of sensitivity and specificity. Some researchers deem elevated CSF red blood counts sufficient to diagnose SAH (Edlow 2003) whilst others require a xanthochromic appearance of CSF supernatant. This latter group is further split into those who deem visual inspection inadequate (Vermeulen, Hasan et al. 1989, Vermeulen 1996, Beetham 2003, Cruickshank, Auld et al. 2008), those who argue against using the spectrophotometric method (Perry, Sivilotti et al. 2006) as well as those who are indifferent to the method used (Vivancos, Gilo et al. 2014, Perry, Alyahya et al. 2015).

There is even discord at the lowest level of abstraction – the spectrophotometry camp itself is split into those who value bilirubin above all other pigments (Beetham 2003, Cruickshank, Auld et al. 2008), and those who are more “colour-blind” in their approach and do not distinguish between oxyhaemoglobin and bilirubin pigments (Vermeulen, Hasan et al. 1989).

It is necessary to identify and address the strengths and weaknesses of the different methods as these will serve as a benchmark against which any alternative test can be judged.

Limitations of the evidence

Vermeulen, Hasan et al. (1989) found persistent xanthochromia by spectrophotometry from 12 hrs to 2 weeks but they defined xanthochromia based on spectrophotometric absorbance patterns of oxyhaemoglobin *or* bilirubin. This

would not meet the criteria required for SAH diagnosis according to the most recent guidelines for CSF analysis (Cruickshank, Auld et al. 2008) and renders their dataset vulnerable to false positive results caused by oxyhaemoglobin contamination following traumatic LPs.

Visual xanthochromia assessment has been repeatedly shown to be an insensitive method to detect blood pigments in the CSF with sensitivities ranging between 27 and 50% (Sidman, Spitalnic et al. 2005, Perry, Sivilotti et al. 2006, Arora, Swadron et al. 2010, Hann, Chu et al. 2015). Despite this, spectrophotometry has not been widely adopted – particularly in North America where a survey of over 800 Hospitals found that 99% of them used the visual method. A subsequent, expanded survey of 2500 hospitals and laboratories in North America found similar results (Edlow 2002, Shah 2002).

Use of the LP is recommended as a safety net, to ensure that the diagnosis of SAH is not missed despite a false negative CT. With this in mind, it is difficult to justify using the visual method of assessment considering its poor sensitivity. Perry, Sivilotti et al. (2006) argue that the higher sensitivity of spectrophotometry for xanthochromia comes at a cost of reduced specificity for *aneurysmal* SAH. They reason that use of spectrophotometry over visual inspection would increase the number of positive results leading to increase rates of angiography and the identification of more incidental aneurysms. They argue that this would “increase patient anxiety and expose patients to unnecessary surgical or investigational complications without benefit”.

In making this argument Perry, Sivilotti et al. expose the empirical shortcoming that plagues research and practice in this field: when diagnosed, it is not possible to confirm that SAH is caused by aneurysm rupture. It may be reasonable to utilise a less sensitive method of CSF analysis (i.e. visual inspection) as Perry argues, but this undermines the rationale for performing the LP in the first place and raises some fundamental questions – what is required of a test for SAH? Is sensitivity or specificity more important and who should make this decision? Is the detection of subarachnoid blood sufficient or must a test also identify an aneurysmal cause – in other words is the test for SAH or aneurysmal SAH? These issues are glossed over when the “LP” is considered a generic test. It is

therefore essential that the performance of the different methods are appraised separately.

Sensitivity and specificity of different methods of CSF analysis

For some investigators in the past, the finding of xanthochromia was the outcome of interest and defined SAH. However, xanthochromia is not specific to SAH. Furthermore, because “benign” SAH can occur, it is more useful to know the sensitivity and specificity of a test for *aneurysmal* SAH.

Recently, Carpenter, Hussain et al. (2016) performed a systematic review and meta-analysis of the diagnostic accuracy of history, physical examination, cerebrospinal fluid tests, computed tomography, and clinical decision rules for spontaneous SAH. They accepted the prevailing gold standard from the literature to requiring the combination of subarachnoid blood (on unenhanced CT, or CSF xanthochromia, or CSF RBCs > 5×10^6/L in the final sample of CSF) in addition to an aneurysm or arteriovenous malformation evident on cerebral angiography. Arguably, this definition of *aneurysmal* SAH shifts the expectation of the LP away from what it is able to achieve (the detection of blood), and demands the detection of an underlying vascular cause which it is not able to do.
Their findings pertaining to the sensitivity and specificity of LP to detect aneurysmal SAH are outlined below along with the relevant methodology used to define the presence or absence of aneurysmal SAH.

Table 3. Summary of Meta-Analysis findings from Carpenter, Hussain et al. (2016)

Risk Factor / (Study Reference)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR, % (95% CI)	Negative LR, % (95% CI)	SAH Criterion Standard	Follow up	SAH Prevalence %
CSF RBC >1000 x 10^6/L							
(Czuczman 2013)	65 (44-83)	79 (72-84)	3.09 (2.09-4.57)	0.44 (0.26-0.75)	Either 1) presence of SAH on imaging; 2) xanthochromia with aneurysm or AVM>2mm; 3) xanthochromia and culture or PCR-negative meningitis	None	11.8
(Perry 2015)	93 (68-100)	91 (88-93)	10.25 (7.73-13.59)	0.07 (0.01-0.49)	Aneurysmal SAH if blood on CT, visual xanthochromia, or any RBC in the final tube of CSF with an aneurysm on cerebral angiography	Phone follow up at 1 and 6-months for all patients without CT or LP; review of chart and coroner's records at study end for same patients	2.3
Pooled Accuracy	76 (60-88)	88 (86-90)	5.66 (1.38-23.27)	0.21 (0.03-1.66)			
Xanthochromia – UK NEQAS							
(Perry 2006)	100 (16-100)	83 (77-88)	4.87 (2.71-8.73)	0.20 (0.02-2.53)	Any one of the following: subarachnoid blood on CT; >5×10^6/L RBC in 3rd or 4th tube of CSF; visible xanthochromia + aneurysm on cerebral angiography	Phone follow up at 1-month for CT-ve LP-ve patients; chart review at 1-month for all patients	0.9
(Gangloff 2015)	100 (48-100)	98 (97-99)	47.67 (26.67-85.20)	0.08 (0.01-1.21)	Presence of any aneurysm and presence of either visual xanthochromia or >5 × 10^6 RBC/L in last CSF tube	None	0.7
Pooled Accuracy	100 (59-100)	95 (93-96)	15.23 (1.58-146.73)	0.13 (0.02-0.83)			
Xanthochromia -- Visual							
(Perry 2006)	50 (1-99)	97 (93-99)	15.57 (3.25-74.54)	0.52 (0.13-2.07)	As stated above	As stated above	0.9
(Dupont 2008)	93 (66-100)	95 (89-98)	19.13 (8.04-45.45)	0.08 (0.01-0.50)	Not specified	None	12.0
(Gangloff 2015)	80 (28-99)	99 (98-99)	62.31 (28.47-	0.20 (0.04-	As stated above	As stated	0.7

			136.37)	1.17)		above	
(Hann 2015)	83 (36-100)	95 (92-97)	16.79 (9.62-29.32)	0.18 (0.03 – 1.05)	Presence of vascular aneurysm on angiogram within 30 days of headache or no repeat ED visit or SAH death in 30 days	Review of Queensland death registry	1.5
(Morgenstern 1998)	52 (30-74)	52 (44-60)	1.09 (0.7-1.7)	0.92 (0.57-1.47)	Either 1) presence of SAH on imaging OR 2) CSF RBC > 1000 with <25% decrement from first to last tube with either visual xanthochromia, SPM xanthochromia, or elevated D-dimer	Phone follow up at mean 24 months	18.6
Pooled Accuracy	71 (56-83)	93 (91-94)	12.56 (2.03-77.67)	0.30 (0.09-1.06)			

LR = Likelihood ratio; RBC = Red blood cells; AVM = Arterio-Venous Malformation; PCR = Polymerase chain reaction; ED = Emergency Department; SPM = Spectrophotometrometry

The findings of Carpenter et al. demonstrate that unless strict UK NEQAS criteria are applied, the sensitivity and specificity of the LP is sub-optimal. Arguably, visual assessment of CSF, or use of the RBC >1000 $x10^6$/L criteria, lack sufficient sensitivity and specificity to justify their use.

Clinical Utility of the LP

Although the strict application of the UK NEQAS criteria for spectrophotometry yields a high sensitivity and specificity, the actual utility of the test is influenced by the prevalence of the disease. As described by Coats and Loffgren, sensitivity and specificity statistics derived from the whole population can be confusing and even be misleading when applied to an individual. The likelihood ratio can be used in this instance and can link pre-test and post-test probabilities according to Bayesian statistical modelling.

Before it was widely available CT was reserved for patients with a high pre-test probability of SAH. But the use of CT has drastically increased since the 1980s. Just over one million CT scans were performed by NHS England in 1996/97 compared to almost 5 million in 2012/13, with no sign of reaching a plateau (COMARE 2014). The availability of CT is now so great that it has become

ubiquitous in clinical practice and is routinely performed prior to LP in suspected SAH - as recommended by guidelines. Assuming the incidence of SAH has remained stable in the UK, this increase in scan use translates into a reduction in the pre-test probability of disease.

The probability of SAH in a patient undergoing CT for SAH was estimated to be in the region of 12% in the late 1990s (Coats and Loffhagen 2006). More recent estimates put that closer to 5% (Carpenter, Hussain et al. 2016). Modern CT is highly sensitive to SAH, so the post-test probability of SAH following a normal CT today is likely to be even lower still. Bayesian logic dictates that this should result in extremely low yield of SAH when LP is performed. This is borne out by the evidence. Brunell, Ridefelt et al. (2013) noted just five cases of SAH (1.1% of LPs) diagnosed by spectrophotometry with 91 LPs needed to identify just one case of SAH. Of these cases, there were no examples of CT negative *aneurysmal* SAH.

Sayer, Bloom et al. (2015) reviewed 1,898 CSF samples taken from patients with suspected SAH and negative CT scans. They found just 92 (4.8%) were positive for SAH according to the UK NEQAS criteria. Of these, only nine (0.4%) had an underlying vascular lesion that could account for the haemorrhage giving the test a positive predictive value of just 7.4% for *aneurysmal* SAH. Importantly, 15.6% of LPs performed were uninterpretable (due to procedure failure) and 13.6% were reported as inconclusive due to large amounts of oxyhaemoglobin potentially masking elevated bilirubin. Therefore, in the course of investigation of CT negative suspected SAH, it is far more likely that an LP will be non-diagnostic than test positive due to subarachnoid haemorrhage from an underlying, treatable vascular lesion.

In their meta-analysis Carpenter, Hussain et al. (2016) pooled data from Perry, Stiell et al. (2011) and Backes, Rinkel et al. (2012), to derive a negative likelihood ratio for a CT (performed within 6 hours) of 0.01 (0.00 – 0.04). Drawing on data from a further three studies (van der Wee, Rinkel et al. 1995, Boesiger and Shiber 2005, O'Neill, McLaggan et al. 2005) they found a pooled negative likelihood ratio of 0.07 (0.03 – 0.17) for a CT performed at any, unspecified time after symptom onset.

Carpenter et al. conclude that only patients with pre-CT likelihood of SAH well above 20% are likely to benefit from an LP after a negative CT scan. Such pre-test probabilities are far higher than the average diagnostic yield of CT (5%) and are unlikely except for severe cases which would not be expected to have a negative CT in the first place.

Today, the probability of disease in the pre-LP population is very low and the criteria for a positive LP is more stringent. This means that the test is unlikely to be positive. Furthermore, even when present, SAH may not be caused by an aneurysm so the relevance of a positive result is further diminished.

The LP may still be useful in some circumstances. For example, high-risk patients presenting after considerable delay may warrant an LP, even if their initial CT scan is normal. However, patient selection does not occur in this way. Instead, the LP is used routinely in current practice which reduces the pre-test probability and undermines its utility.

Summary

Despite the dogma, the clinical utility of LP is questionable. The assertion by guidelines that the test should be mandatory in CT negative cases is based on outdated evidence and does not account for variable definitions of positive LP results, many of which lack sensitivity and specificity. Although the test may be of use in some clinical scenarios, the time may be fast approaching to change the diagnostic pathway.

Before proposing an alternative test to the LP, it is necessary to understand the clinical landscape for which it is destined. This means understanding the preconceptions which underpin clinician behaviour and the requirements a new test would need to fulfil. Once this has been achieved an alternative diagnostic test can evaluated against these criteria to see if it has potential clinical utility.

To be a desirable improvement upon the LP in the investigation of suspected aneurysmal SAH, a test would need to be highly sensitive and less invasive. It is not clear how these two factors are prioritised by clinicians on the front-line. It seems apparent from the research already discussed that LP is regarded by some as an essential gold standard test in the diagnosis of aneurysmal SAH. Spectrophotometric assessment of CSF for bilirubin can be an accurate marker of SAH provided it is analysed according to strict guidelines. However, in practice its performance is weakened because of the likelihood of inconclusive results, patient refusal and a very low pre-test probability.

To surpass these limitations an alternative test should complement the sensitivity of CT in the same way that LP does, be well tolerated by patients and, ideally, non-invasive.

Modern CT is becoming accepted as a reliable test in the first 6 hours with many authorities now advocating the LP is not needed in this time frame (Perry, Stiell et al. 2011, Edlow and Fisher 2012, Blok, Rinkel et al. 2015, Dubosh, Bellolio et al. 2016). Unfortunately, a significant number of patients present outside this time frame and this group are likely to have milder symptoms and low volume haemorrhage which is less evident on CT. Therefore, an alternative, supplementary test would need to shore-up the deficiencies of the CT outside the 6-hour timeframe.

Researchers have proposed that non-invasive vascular imaging could be utilised in place of the LP (McCormack and Hutson 2010) and improvements in cross-sectional angiography now make this a viable alternative with a pooled sensitivity of 98% for aneurysm detection by CT Angiography (CTA) according to a recent meta-analysis (Westerlaan, van Dijk et al. 2011). However, the proposal that CTA could replace the LP in suspected CT negative SAH has been criticised on the basis that it shifts the primary objective of investigation away from diagnosis of a bleed and towards diagnosis of a vascular lesion which may or may not be responsible for the patient's symptoms. Given the relatively high incidence of asymptomatic aneurysms in the normal population (approximately 2.5%), this strategy has the potential to misdiagnose incidental aneurysms as causative

lesions. This could lead to harm from unnecessary surgical or endovascular treatment, as well as anxiety and insurance implications for patients receiving the diagnosis (Edlow 2010).

Furthermore, angiography is not truly a replacement or alternative to the LP because it is already an integral step in the investigation pathway. CTA use in the diagnostic pathway in place of an LP is equivalent to LP omission rather than a bona fide alternative. To be considered a genuine alternative to the LP, a test should complement the diagnostic pathway by demonstrating haemorrhage not evident on CT.

MRI in SAH

Early studies using low magnetic field-strength systems showed promise for MRI in the detection of subacute subarachnoid haemorrhage. Ogawa, Inugami et al. (1995) demonstrated that MRI surpassed CT in detecting subacute / chronic subarachnoid haemorrhage using a 0.5T MRI system. In this study 42 clinical cases of confirmed SAH (using CSF xanthochromia assessment as the reference standard) were evaluated using T1, proton density (PD) and T2, and moderately T2-weighted MR sequences. Subacute / chronic SAH was detected in 90% using PD compared to 46% for CT.

Noguchi, Seto et al. (2000) investigated the threshold sensitivity of MRI and CT to detect acute haemorrhage by performing an *in vitro* study using phantoms containing predetermined mixtures of whole blood and synthetic CSF. They demonstrated that below a 27% dilution, whole blood was isodense to normal grey matter on CT, thereby nullifying the intrinsic contrast required for detection. MRI pulse sequences were better able to retain the contrast between grey matter and blood-stained CSF at more dilute levels – demonstrating signal differences between cortex and whole blood at dilutions as low as 9%.

Haem-sensitive MRI

Depiction of subacute and chronic haemorrhage can be further optimised by the use of “haem sensitive” pulse sequences. T2* Gradient Recalled Echo (T2*-GRE) sequences exploit the paramagnetic properties of haemoglobin and its metabolites and can detect deoxyhaemoglobin and haemosiderin with a sensitivity superior to CT (Mitchell, Wilkinson et al. 2001). T2* imaging has also been shown to outperform CT in the subacute time-frame (Mitchell, Wilkinson et al. 2001, Yuan, Lai et al. 2005) although some researchers have failed to replicate these findings (da Rocha, da Silva et al. 2006).

Susceptibility Weighted Imaging (SWI) incorporates phase-dependant effects with conventional T2* magnitude signal and has been shown to further improve detection haemorrhage from a variety of causes including: traumatic SAH (Wu, Li et al. 2010); microhaemorrhages (Goos, van der Flier et al. 2011, Charidimou, Jager et al. 2012); PRES (McKinney, Sarikaya et al. 2012); Traumatic Brain

Injury (Babikian, Freier et al. 2005, Ashwal, Babikian et al. 2006, Sigmund, Tong et al. 2007, Akiyama, Miyata et al. 2009); Moyamoya disease (Mori, Miki et al. 2008) and haemorrhage/ haemorrhagic transformation in stroke (Chalela, Kidwell et al. 2007, Lu, Li et al. 2012).

The superiority of SWI over CT in the detection of subacute SAH has been demonstrated by some researchers (Verma, Kottke et al. 2013, Hodel, Aboukais et al. 2015). However, when used to detect acute SAH (i.e. within days of haemorrhage) some researchers have shown parity between CT and susceptibility weighted imaging techniques (Yuan, Lai et al. 2005), others have found mixed results (Fiebach, Schellinger et al. 2004, Kidwell, Chalela et al. 2004) but no research demonstrates clear superiority of SWI or T2* imaging over CT in the acute stage following SAH.

Fluid Attenuated Inversion Recovery: FLAIR

The Fluid Attenuated Inversion Recovery (FLAIR) sequence is designed to null fluid signal during image acquisition. Consequently, in a normal image CSF appears black. In SAH, the presence of blood in the CSF prevents normal attenuation of CSF signal making any area contaminated with blood appear bright (see figure 10, page 83).

The utility of FLAIR in acute SAH was suggested in a preliminary case report by Noguchi, Ogawa et al. (1994). Subsequently, a number of researchers have demonstrated its utility in the detection of acute SAH. Unlike SWI, FLAIR imaging has demonstrated superiority over CT in the acute stages of SAH (Chrysikopoulos, Papanikolaou et al. 1996, Mohamed, Heasly et al. 2004, Yuan, Lai et al. 2005, da Rocha, da Silva et al. 2006, Verma, Kottke et al. 2013) although it has not proven sufficiently sensitive to replace the CT/LP paradigm (Mohamed, Heasly et al. 2004).

Others have reported shortcomings of FLAIR imaging in SAH evaluation due to the presence of artefactual sulcal hyperintensity which may be caused by supplemental oxygen, CSF pulsation, and vascular pulsation and may mimic acute SAH (Stuckey, Goh et al. 2007). These shortcomings have been partly

overcome by applying 3D volume acquisition techniques (Kallmes, Hui et al. 2001, Lummel, Schoepf et al. 2011) which eliminates pulsation artefact making it possible to reliably diagnose small regions of haemorrhage.

Advanced pulse Sequences

More recently imaging studies have demonstrated the potential utility of Double Inversion Recovery (DIR) sequences in SAH detection. Double inversion recovery imaging employs inversion recovery pulses in the same manner as FLAIR but allows nulling of an additional compartment on the basis of its T1 value alongside the CSF compartment. Hodel, Aboukais et al. (2015) utilised DIR to suppress signal from white matter and CSF in a group of patients with proven subacute SAH and demonstrated superiority of DIR above CT, SWI and 3D FLAIR.

Subarachnoid Haemorrhage imaging research demonstrates the potential for MRI to be used as a complimentary non-invasive imaging test to detect SAH when suspected following normal CT scan results. In particular the study protocol of Hodel, Aboukais et al. (2015) combines sequences with proven superiority to CT in the subacute timeframe (SWI), as well as sequences which can be complementary to CT in the acute timeframe (FLAIR and DIR). However, this study included patients with poor grade SAH (Glasgow Coma Scale range 10-15), scanned in a late subacute phase of the illness (14-16 days after haemorrhage). Furthermore, this study includes patients scanned following treatment with endovascular coiling which could result in degradation of imaging.

To be of use as a non-invasive alternative to the LP, this imaging protocol needs to be validated in a cohort of patients in whom the test would be useful. Namely, patients of good grade (GCS 15), and during their initial acute presentation.

To date, no prospective study has evaluated the ability of DIR, SWI and 3D-FLAIR to detect spontaneous/small volume SAH in the neurologically intact population who constitute a major diagnostic dilemma regarding SAH investigation. The final part of this thesis addresses this knowledge gap.

Summary

When investigating the acute onset headache, clinicians consider aneurysmal SAH the diagnosis not to miss. Clinical diagnosis is unreliable so further investigations are deemed necessary to confidently rule out this life-threatening diagnosis.

The best tests currently available to diagnose SAH include the lumbar puncture (with analysis of the CSF for bilirubin), and imaging of the subarachnoid space for the existence of blood/ blood degradation products. Both methods lack sensitivity to diagnose SAH in certain circumstances, but the limits of sensitivity for each technique are difficult to ascertain empirically. This field of research suffers from the limitation that there is no true gold standard test and no methodology is able to accurately and categorically define aneurysmal SAH in any individual.

Ever since its widespread availability, CT has become the first line test in SAH investigation but it is known to lack sensitivity, especially in the subacute stage. International and national guidelines deem the LP to be a pre-requisite for investigation if initial CT imaging is negative. However, practice is often discordant with these guidelines. The LP is frequently omitted and when performed the method of CSF interpretation is variable and often unreliable.

The reason for discordance between recommendations and practice is unclear but may reflect the invasiveness of the LP combined with perceived poor clinical utility. In modern day practice a large number of LPs need to be performed to detect a small number of SAH cases. Even when detected, an underlying vascular cause is rarely found and treatment rarely changes.

Modern-day CT has improved since the early studies and appears to be highly sensitive in the acute stages of SAH. This has led a number of authorities to call for a change in the guidelines so that LP need not be performed when a normal CT is obtained within 6 hours of symptom onset. However, if the guidance is changed, a majority of patients still present outside the 6-hour window and clinicians will still struggle to balance the risks and benefits of performing an invasive test of uncertain clinical utility.

Patients and doctors would benefit from an alternative non-invasive test in SAH investigation but it is not clear how such a test would be perceived. Development and validation of a new diagnostic test in SAH is logistically difficult because of the rarity of the disease and the lack of a suitable gold standard test.

MRI could compliment the sensitivity of CT, especially in the subacute phase, and could be a useful non-invasive alternative to LP. However, MRI may not be acceptable to clinicians managing patients, or to those responsible for formulating guidelines, given the perceived benefits of the LP. The aim of this thesis is therefore threefold:

1) To establish whether the current practice of SAH investigation deviates from recognised guidelines
2) To establish clinician's opinions regarding appropriate investigation of SAH with particular attention to their perceptions of the utility of LP, and the demands required of a non-invasive alternative
3) To demonstrate superior sensitivity of MRI over CT for the detection of SAH in a cohort of treatment naïve patients presenting acutely.

PART I: Investigation of clinician behaviours in SAH investigation

Background

A systematic search of the pubmed database supplemented with a review of references yielded a total of six English language papers published between 2002 – 2016 detailing the frequencies of lumbar punctures performed in CT negative suspected SAH. Of these studies, the greatest adherence to guidelines was observed by Mehrotra, Sookhoo et al. (2010) who found 64% of patients in their unit (the Royal Sunderland Hospital) went on to have an LP to test for the presence of xanthochromia when an initial CT was normal. In contrast, the frequency of LP was as low as 22% in an equivalent Canadian cohort of 296 patients reviewed by Perry, Stiell et al. (2002), the largest of the populations studied. In total, these studies report on 1,274 patient episodes in which CT was performed for suspected subarachnoid haemorrhage. Only 50% of patients went on to have an LP.

These findings are supported by self-reported practice preferences of clinicians participating in surveys. Perry, Eagles et al. (2009) found that just 57% of 1,149 emergency physicians from Australia, Canada, the United Kingdom and the United States felt a negative CT should always be followed by a lumbar puncture. Similarly, 47% of 878 Australasian Emergency Medicine clinicians and trainees responding to a similar electronic survey agreed, or strongly agreed, that a negative CT brain scan performed within 6 hours of headache onset was sufficient to exclude a diagnosis of SAH (Rogers, Furyk et al. 2014).

The sampled populations published in the literature include tertiary neuroscience centres and district general hospitals in the UK, US, Australia and Canada. Before investigating the underlying reasons for these observations in our own population, it is necessary to establish whether these findings are replicated in our population of interest.

To this end, a representative sample of health care institutions was selected for study. For practical purposes three London based NHS hospitals were selected including: Kings College Hospital NHS Foundation Trust, The Royal London

Hospital (Barts Health NHS Trust), and University College London Hospitals NHS Foundation Trust.

Aim

1. To determine how commonly LP is performed in cases of suspected spontaneous SAH when the initial CT is negative.

2. To determine the reasons for omission of LP following a negative CT head scan

Methodology

A service evaluation of the SAH investigation pathway was conducted according to local clinical governance guidelines at each of the above institutions.

The picture archiving and communications system (PACS) was searched for any CT head scan performed containing the terms “SAH”, “Subarachnoid Haemorrhage” or “Subarachnoid Bleed” in either the text of the radiology report or the “clinical information” or “clinical question” fields of the CT request. The search was limited to CT head examinations performed between 1st January 2015 and 31st March 2015. Results of the initial search were screened and requests that did not explicitly query spontaneous subarachnoid haemorrhage as a diagnosis were excluded.

Patients with repeat scans performed within the three-month evaluation period were included at both time points.

Basic patient data (age, sex, scan date) was collected and the outcome of the scan was recorded as either “negative for SAH”, “positive for SAH”, “alternative diagnosis”, “equivocal for SAH”. If no CT head result was available this was recorded.

Discharge summaries, clinical admission notes and biochemistry results were then reviewed to determine what subsequent action had been taken. In cases where an LP had been performed the result was recorded. In cases without a

subsequent LP result, any reason for this was also noted according to the following categorisation:

1. Patient declined
2. SAH suspicion revised on subsequent review (SAH diagnosis stated as unlikely or alternative diagnosis provided)
3. Patient improved, no other reason given
4. No reason documented / no formal diagnosis on discharge
5. Missing data

Results were tabulated in Excel for mac (version 16.10) and exported to Statplus (version 6) for calculation of descriptive statistics.

Results

Sample Characteristics

A total of 188 cases were reviewed from all institutions combined with a mean age of 43 (standard deviation 16.6), 75 males and 113 females.

CT results

Of the 188 patients for whom the CT was performed, 177 (94%) were negative. In 5 cases a diagnosis of SAH was made by the reporting radiologist on the basis of the CT appearances. In a further 5 cases an alternative diagnosis was made on CT which adequately explained the clinical presentation and effectively excluded SAH. In one case the reporting radiologist gave an equivocal result, this was treated as a negative result for the purposes of this study as it did not enable a change in management or obviate the need for LP according to practice guidelines.

LP Results and Omissions

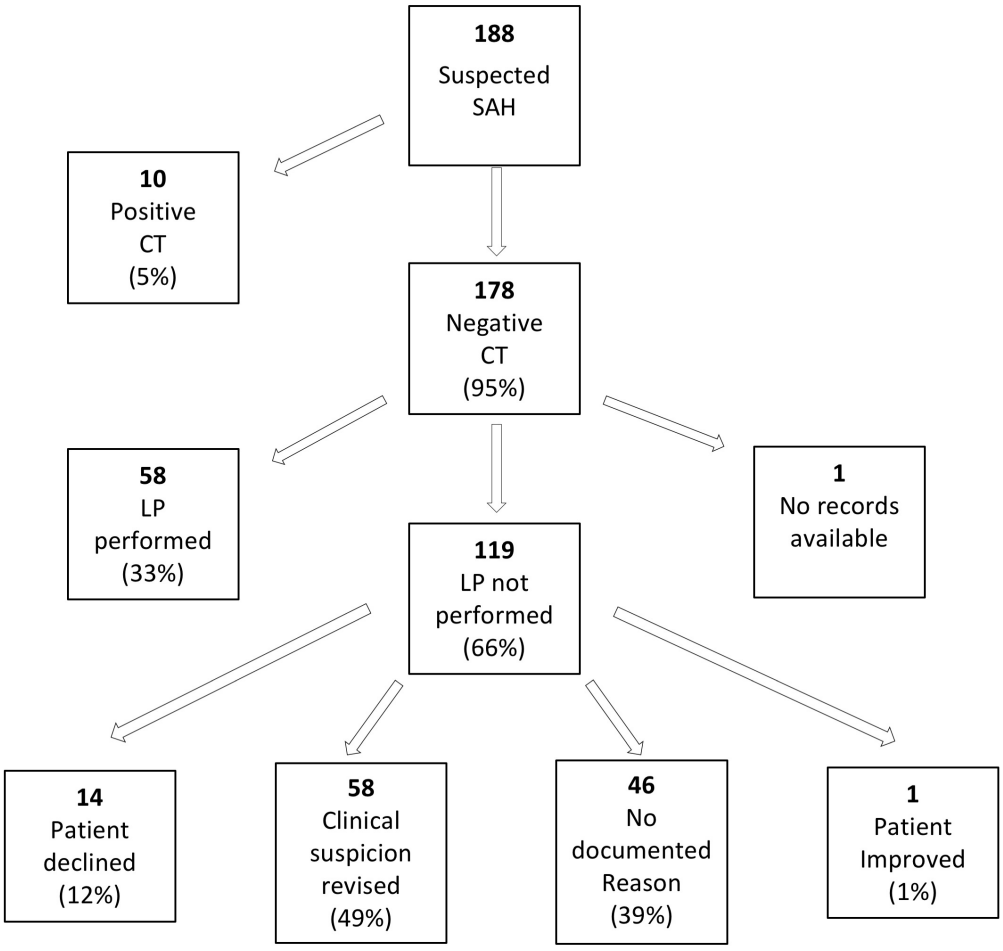
In one case the electronic medical records system did not show any notes pertaining to the patient encounter following the CT. This patient was excluded from further analysis. In all other cases, it was possible to determine whether or not an LP had subsequently been performed, although the reason for omission was not always documented.

Fifty-eight (33%) of the 178 patients with negative or equivocal CT results had an LP. The LP was reported as normal in 46 of the 58 patients tested (79%), inconclusive in 8 (14%) and provided an alternative diagnosis in 4 (7%). There were no cases of SAH diagnosed on the basis of a normal CT and positive LP. Assuming that there were no false negative cases in the cohort, the pre-CT probability of SAH in the sample can be calculated as 2.6% (5/188 x 100%).

Reasons for LP Omission following a negative CT scan

A revised clinical suspicion of SAH was explicitly stated in the records of 58 patients (49%) in whom LP was omitted. A further 14 patients were documented to have declined the LP procedure following a negative CT result. Of the remaining 47 patients with negative CT results and omitted LPs, 46 cases had no stated reason. In one case “clinical improvement” was cited as the reason for discharge (see figure 4).

Figure 4. Flow chart demonstrating the different diagnostic pathways undertaken in the sample. Percentages given to the nearest percent



The findings of the local service evaluation support observations of previously published national and international studies that patients suspected of SAH infrequently go on to have a lumbar puncture despite this being the recommended diagnostic workup according to published guidelines. The finding that 33% of eligible patients undergo LP in this clinical scenario falls within the 22 – 64% range established in previous publications.

The retrospective methodology of the current study is largely similar to that of the literature. Although some of the published studies employed prospective recruitment, the outcome data was always retrospectively generated. Indeed, if the patients were followed longitudinally by a research team, this additional scrutiny could have influenced the behaviour under study, thereby biasing results and inhibiting the ability to obtain a representative sample of clinical practice. Retrospective data collection limited the ability to establish the underlying rationale of management. This was overcome to some extent by analysis of clinical notes which did elucidate the clinical reasoning in some cases, however this was limited by the completeness of clinical documentation. In over one third of cases there was no documented reason for omitting the LP.

No long term clinical follow-up or review of death registry was performed, so it is possible that patients with missed aSAH represented to another institution (or to the same institution outside the period of study). Nevertheless, given the low incidence of disease, this is unlikely and would not be expected to significantly change the pre-CT probability of aSAH of 2.6% in the cohort.

Deviating from recommended practice exposes a clinician to litigation. Clinicians would therefore be motivated to document cases where patients refused to undergo an LP as this could exonerate them in the event of a subsequent missed diagnosis. It is therefore unlikely that patients without a documented reason for LP omission would have declined the procedure. However, no reliable assumptions can be made about this group of patients based on the data available.

It is not possible to determine why clinicians downgraded their suspicion of SAH when reviewing patients after their CT scan. It is possible that the CT result itself served as a *fait accompli* for some clinicians with no intention to investigate further - despite the mainstream opinion that CT is insufficient to reliably exclude SAH. Alternatively, it is possible that the clinical indication that prompted the CT request was exaggerated to justify performing the examination and that a normal scan provided sufficient reassurance to facilitate discharge.

Due to the limitations of medical documentation, it was not possible to determine whether the post-CT clinical review was carried out by a different clinician, or a senior clinician, or if the alternative clinical assessment was any more valid than the assessment which raised the suspicion of SAH to begin with.

The results replicate the findings reported in the literature that the yield from LP is low, equivocal results are common, and patients frequently decline the procedure - criticisms previously cited by authors proposing a move away from the mandatory use of LP in SAH diagnosis (Morgenstern, Luna-Gonzales et al. 1998, Foot and Staib 2001, Brunell, Ridefelt et al. 2013, Ditta, Galea et al. 2013).

Our cohort was unable to demonstrate SAH which were falsely negative on LP because LP was only performed in CT negative cases. However other studies have demonstrated that the LP has imperfect sensitivity. In their evaluation of the LP as a gold standard test for SAH, Stewart, Reuben et al. (2014) showed that the LP was equivocal in 9/169 (5%) patients, two of whom were subsequently determined to be positive cases based on angiography findings. Furthermore, in their sample of 244 patients Stewart, Reuben et al. reported LP failure in 10 patients due to technical difficulty, insufficient sample, or patient refusal.

An equivocal result is not the same as a false positive however in order to characterise test performance, equivocal results need to be categorised as either positive or negative to allow the calculation of specificity and sensitivity. This is illustrated by Hann, Chu et al. (2015) who found large differences in calculated sensitivity and specificity for visually inspected CSF analysis depending on the categorisation of inconclusive results. When inconclusive results were categorised as positive, sensitivity was 83.3% with specificity 95.0%. When the

equivocal results were categorised as negative the sensitivity was markedly reduced (50.0% with a specificity of 99.0%).

Our finding that 14 patients declined LP (12%) approximates the opt out rate reported by (Morgenstern, Luna-Gonzales et al. 1998) who found 11% (10 of 89) of patients refused to undergo the LP after being recruited as into their study protocol.

Although the LP has achieved status as a benchmark test, its utility is of questionable value when there is a low pre-test probability such as the CT-negative cohort in which it is used. The sensitivity of a test indicates its ability to detect disease, whereas the positive predictive value (PPV) and negative predictive value (NPV) of a test informs the clinical management of a patient based on the test result (Weinstein, Obuchowski et al. 2005). The difference between these measures in the context of SAH may help explain the divergence of clinical practice from published guidelines.

High sensitivity of CT scanning for SAH means that patients with normal scans have a small risk of having the disease. Subsequent use of a test with low specificity will generate a significant proportion of false positive results, such that even if the test is positive the patient is unlikely to have the disease. Wood, Dimeski et al. (2005), demonstrated this effect. They defined *aneurysmal* SAH in a CT negative cohort as the presence of uniform bloodstaining of the CSF across serial samples with visual xanthochromia and a positive angiographic finding. Using this definition, they found a high false positive rate using CSF spectrophotometry to diagnose aneurysmal SAH with a specificity of 75%. Given the low prevalence of disease in the CT negative population this resulted in a positive predictive value of 3.3%[2]. In other words, when the CSF is sampled following a negative CT head scan, 96.7% of patients with a positive spectrophotometry result will not have suffered aneurysmal SAH. They conclude

[2] The spectrophotometry absorbance criteria used by Wood et al. did not distinguish between oxyhaemoglobin and bilirubin and could therefore misclassify a traumatic tap as positive result

that this makes the LP an unsuitable tool with which to select patients for further investigation, particularly when it exposes the patient to a risk of morbidity.

Coats and Loffhagen (2006) illustrate the utility of the LP as a test for SAH using a Bayesian analysis of the diagnostic pathway. They demonstrate that if the pre-test probability of SAH is 5% and CT is done within 12 hrs of the headache (when it is most sensitive) 1000 patients would have to undergo an LP in order to find one patient with a SAH. As the pre-test probability increases (e.g. when CT is done later and is a less sensitive test) then the utility of the LP increases and fewer LPs are required to detect a SAH. They argue that there may be a threshold point at which the accumulated costs of all the LPs required to detect a single case of SAH outweigh the benefits.

Taken together these two findings illustrate the limited utility of the LP: even when a large number of LPs are performed the rare positive results cannot be relied upon to indicate disease.

With this in mind it is easy to see why the LP is so often omitted. It is unlikely to impact patient outcome based on the low yield and high probability that the patient is free of disease even when the test is positive.

The relative ease with which it is possible to obtain a CT scan in the institutions tested may have also have influenced the decision-making process of clinicians. Compared to cranial CT, an LP is more difficult to obtain, especially for ED staff in the UK who may need to arrange admission in order for the procedure to be performed. Bed availability and ED workload factors could have biased the decision to perform an LP but are unlikely to have influenced the decision to perform a CT which is a quicker and more accessible resource at the institutions studied.

Limitations

There are a number of limitations to the service evaluation described above. The retrospective nature of the investigation resulted in a reliance on clinical records which were sometimes incomplete and resulted in gaps in the data. This problem is not limited to the evaluation presented here and is also evident in the published

literature. However, the primary purpose of the evaluation was to establish current practice and the methodology offered an efficient means to fulfil this goal.

Conclusion

Only a third of patients investigated for subarachnoid haemorrhage in three large London-based neuroscience centres proceeded to LP following a negative CT. This supports published findings that indicate LP uptake in the range of 22 – 64% of cases. The reason for low use of LP is only partly explained by patient refusal. A revision of the clinical assessment was the most common explanation but over a third of cases had an LP omitted for no specified reason.

Effective modern medical care is predicated on medical technological developments, their subsequent dissemination into the wider clinical community and finally, their use by practicing clinicians and patients. Failure of any link in this chain invalidates all prior steps and negates the potential benefits. This is of particular relevance when considering the development of a new diagnostic tool as its potential utility would only be realised if it is acceptable to clinicians and patients.

The benefit of a new diagnostic technique could be outweighed by perceived downsides and preclude use by the clinical community. Downsides of a test could include objective factors (such as test accuracy and cost) or more subjective factors such as invasiveness, ease of use and risk-tolerance of the patient / clinician. The use of a test would therefore be determined by a combination of all these factors.

It would be useful know what these value judgements are before developing a new diagnostic tool so that it is certain to be valued by clinicians and patients in principle, before being validated in technical performance. For example, if the clinical community shared the expectation that MRI in SAH must achieve 100% sensitivity as a diagnostic test, then the discovery of a single false negative result would seriously undermine its acceptability. In reality, there is likely to be a trade-off between a number of test attributes including sensitivity, specificity, availability, cost, ease of use, reliability and how time-consuming it is. When

judging any new test, it is therefore also necessary to compare these attributes to those of the existing standard.

The findings described above demonstrate that clinicians frequently diverge from recommendations for SAH investigation. It is now possible to investigate the reasons for this clinical behaviour within our sample, in the knowledge that it is representative of practice described elsewhere in the literature.

PART II: Survey

Subarachnoid Haemorrhage Guidelines and Clinical Practice: A Cross-Sectional Study of Emergency Department Consultants' and Neuro-Specialists' Views and Risk Tolerances

Although guidelines are not "railroads" for clinicians to follow (Tingle 2002), omission of LP in suspected SAH diagnosis has been widely criticised (Schofield 2004, Mehrotra, Sookhoo et al. 2010, Steiner, Juvela et al. 2013, Martin, Teo et al. 2015), and attributed to a lack of awareness and education (Schofield 2004, Muhammed, Teubner et al. 2010). However, the role of LP has been called into question due to reported low specificity, low clinical impact, low diagnostic yield, and improved sensitivity of modern CT (Morgenstern, Luna-Gonzales et al. 1998, Boesiger and Shiber 2005, Wood, Dimeski et al. 2005, Gee, Dawson et al. 2012, Brunell, Ridefelt et al. 2013, Ditta, Galea et al. 2013, Migdal, Wu et al. 2015, Sayer, Bloom et al. 2015). Doctors are also known to vary in their tolerance of risk and uncertainty which may influence management decisions (Holtgrave, Lawler et al. 1991, Pines, Hollander et al. 2009, Pines, Isserman et al. 2010). The low LP rate in suspected SAH may therefore represent widespread disagreement with guidelines and differences in risk tolerance of misdiagnosis. A fear of LP related complications may also dissuade clinicians from performing or recommending the procedure (Migdal, Wu et al. 2015).

Guidelines for SAH investigation have been shown to be relatively risk intolerant compared to the recommended investigation of other potentially fatal conditions presenting to the emergency department e.g. pulmonary embolism (PE) and acute coronary syndrome (ACS). Guidelines for suspected PE and ACS allow small but non-zero calculated risk end points, whilst SAH guidelines afford no misses (Pines and Szyld 2007). ED clinicians habituated to accept small risks of misdiagnosis for common emergency presentations (such as PE and ACS), may be more willing to accept similar risks in SAH work-up compared to their neuro-speciality colleagues (i.e. Neurologists, Neurosurgeons and Neuroradiologists). Given that patients with suspected SAH are typically managed by emergency

physicians (Davenport 2004), any such variation in risk appraisal could help explain the frequency of LP omission.

Aims

The purpose of this study is twofold:

(1) to survey clinicians' analysis of risk and benefit related to investigation of suspected acute spontaneous subarachnoid haemorrhage

(2) to establish whether published guidelines reflect current professional opinion, and to characterise any variation between ED clinicians and neuro-specialists

The null hypothesis is that ED clinicians are no more risk tolerant than neuro-specialist consultants.

Given an LP omission rate of between 40% and 50% in the UK, at least 40% of ED clinicians are expected to disagree with the guideline stating that LP is required in CT negative cases.

Methodology

No appropriate validated instruments were available to measure risk tolerance for missed SAH diagnosis. A questionnaire was designed for this purpose according to principles described in detail elsewhere (Boynton and Greenhalgh 2004, Rattray and Jones 2007). The questionnaire underwent initial trial use by consultant and trainee clinicians in the relevant specialities. Changes were made to wording, question format, and layout following this exercise.

Each question was devised to investigate clinicians' views on different aspects of the diagnostic process: clinical risk-factors; LP complications; risk-tolerance for misdiagnosis; sensitivity requirements of diagnostic tests; risk-benefit appraisal for diagnostic tests; and investigative inertia, i.e. the propensity to pursue a diagnosis due to referral bias rather than personal appraisal. Whilst piloting the questionnaire, it became apparent that respondents could be identified if they provided their age, gender and specialty. Demographic details were therefore limited to include age range (<40, 41-50, 51-60, >60) and specialty but not gender.

Risk tolerance was measured using a short vignette describing an otherwise healthy, 40-year-old adult, presenting with a worst-ever “thunderclap headache”. Participants were asked to give the post-test probability of missed SAH that they would accept before stopping further investigations. Respondents were told that the pre-CT probability of SAH was ten percent, in line with similar clinical scenarios in the published literature (Edlow and Wyer 2000).

The primary objective of this study was to investigate patterns of risk tolerance and guideline agreement between neuro-specialists and emergency physicians. A lack of validated instruments and relevant preliminary data prohibited a power calculation. We opted to sample two groups (neuro-specialists and emergency physicians) comprising a quota target of 50 respondents, half from each group. Consultant neurosurgeons, neurologists, neuroradiologists and emergency clinicians were approached at four large NHS Trusts with tertiary neuroscience services: UCLH, Kings College Hospital, Queens Hospital Romford and Charing Cross / St Mary’s Hospitals. London Trusts were chosen to reduce the influence of regional variations and to reflect the practices established in the service evaluation described earlier. The inclusion of additional hospitals not sampled in the previous study was deemed necessary in order to provide a sufficient number of completed questionnaires.

A written questionnaire was devised in preference to an electronic survey because of concerns that electronic correspondence would be missed or ignored amongst the large volume of email received by NHS consultants. The questionnaire is shown in Appendix 2.

Ethical approval was granted by the UCL research ethics committee. Permission to conduct the survey was then sought from the clinical lead in each department. Invitations to participate were communicated by telephone, e-mail, and in person wherever possible in order to optimise participation. Secretarial staff were approached to help disseminate the questionnaires and e-mail reminders were sent to eligible consultants where necessary.

Statistical analysis

Data were entered into an Excel spreadsheet (Excel for Mac, 2011). The significance of group differences was calculated using Chi squared statistical tests within Excel. The statistical package (StatPlus) was used for descriptive statistics and for the t-test statistic where appropriate.

Results

A total of 58 consultants completed the questionnaire including 23 ED clinicians and 35 neuroscience specialists. Overall the response rate was 34% with proportional participation by both subgroups (35% for the neuro-specialists compared with 32% of ED physicians). The median age range was 41-50 years and consultants had a median of 16-25 years of post-graduate experience. The gender of participants was not available for reasons described above. See tables 6 and 7 in Appendix 1 for a full breakdown of respondents by institution, age and speciality. A total of 12 questions were omitted in full, or in part, by the 58 respondents (1.5%). A further 22 responses (2.7%) were excluded from analysis because they were inconsistent or incompatible with the question asked indicating a misunderstanding or miscommunication of the question.

Seventeen ED clinicians and 30 neuro-specialists indicated their risk tolerance for missed SAH diagnosis by recording the highest post-test probability at which they would stop investigations to diagnose SAH (Appendix 2, Question 10). There was a significant difference in the mean scores between groups ($p = 0.03$) with the ED clinicians' risk tolerance almost three times higher than the neuro-specialists' (2.8% [SD 3.3] vs 1.1% [SD 1.9]). Neuro-specialists were also more likely to advocate routine LPs compared to ED clinicians (74% vs 39%, $p = 0.01$).

Seventy percent of consultants agreed with current guidelines which stipulate that an LP is mandatory in suspected SAH if the initial CT is negative (question 4a). There was a significant difference between the ED and neuro-specialist groups in this regard with a majority of the ED group disagreeing with guidelines (57%) compared to a minority (11%) of neuro-specialist consultants ($p < 0.001$). ED clinicians were also more inclined to omit the LP if a negative CT had been obtained within six hours of headache onset (35% vs 3%, $p = 0.002$, question 4b). ED clinicians also required a higher pick-up rate to justify the routine use of

LP compared to their neuro-specialist colleagues (question 6), but this difference did not achieve statistical significance.

There was no statistically significant difference in the estimates of LP-related complications between the two groups (question 7) with a median estimate of risk from both ED clinicians and neuro-specialists in the “1 in 200” range (see figure 8).

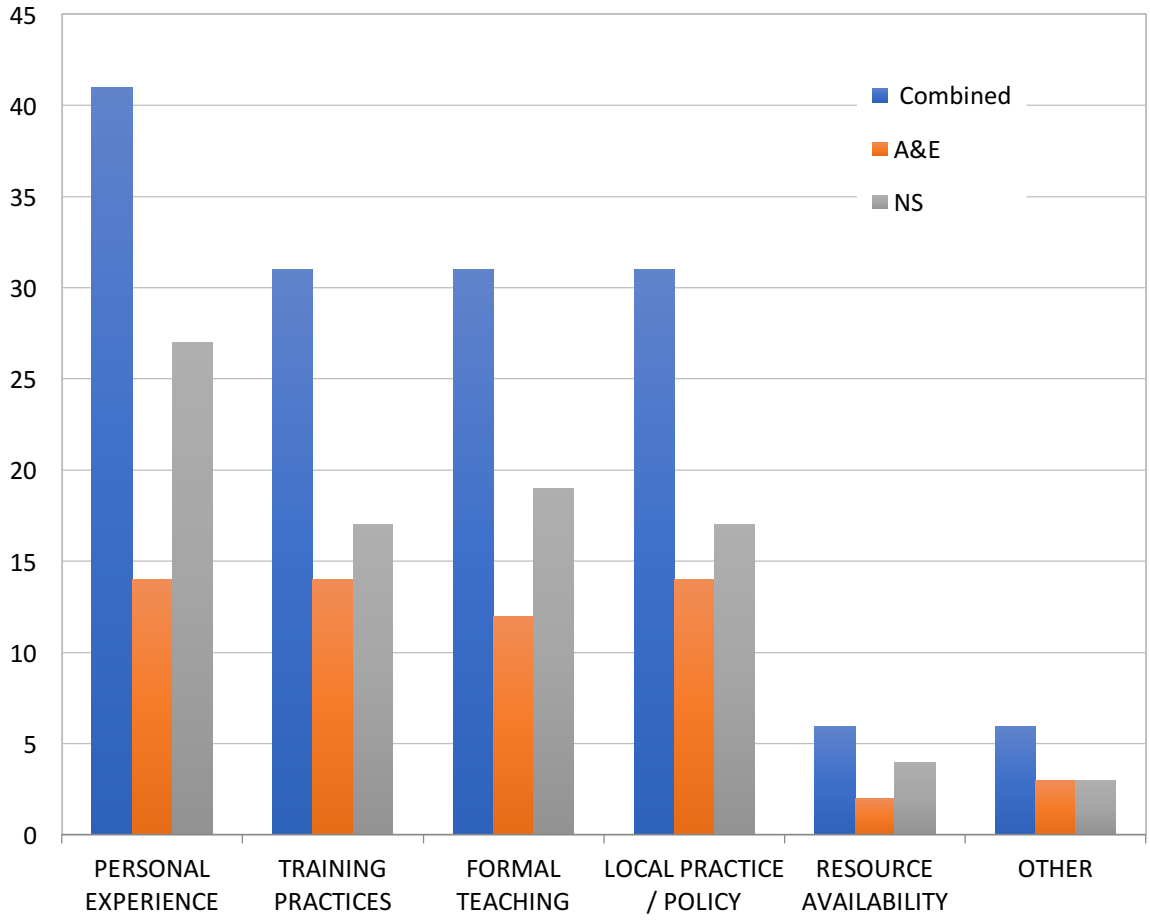
Table 4. Clinicians’ risk-benefit appraisals

Question / Dimension	All Clinicians Combined (n=58)	ED Physicians (n=23)	Neuro-specialists (n=35)	p Value
LP mandatory “No”	17 (30%)	13 (57%)*	4 (11%)	
LP mandatory “Yes”	40 (70%)	9 (39%)*	31 (89%)	**0.0001**
LP omitted when CT < 6hrs “No”	46 (84%)	15 (65%)	31 (89%)◊	
LP omitted when CT < 6hrs “Yes”	9 (16%)	8 (35%)	1 (3%)◊	**0.0017**
Routine LP justified? “No”	23 (40%)	14 (61%)	9 (26%)	
Routine LP justified? “Yes”	35 (60%)	9 (39%)	26 (74%)	**0.007**
Investigative inertia “No”	45 (78%)	20 (87%)	25 (71%)	
Investigative inertia “Yes”	13 (22%)	3 (13%)	10 (29%)	0.2
Required LP pick up rate: >1 SAH per 100 LPs	25 (44%)	12 (52%)	13 (38%)*	
1 SAH per 101-500 LPs	19 (33%)	8 (35%)	11 (32%)*	
1 SAH per >500 LPs	13 (23%)	3 (13%)	10 (29%)*	0.3
Risk-benefit trade-off † Non-invasive “Yes”	12 (21%)	8 (38%)‡	4 (11%)	
Non-invasive “No”	44 (79%)	13 (62%)‡	31 (89%)	**0.018**
Quicker test “Yes”	5 (9%)	2 (10%)‡	3 (9%)*	
Quicker test “No”	50 (89%)	19 (90%)‡	31 (89%)*	0.9
Cheaper test “Yes”	5 (9%)	2 (10%)‡	3 (9%)*	
Cheaper test “No”	50 (89%)	19 (90%)‡	31 (89%)*	0.9
Experience of previous missed SAH “Yes”	52 (91%)	21 (91%)	31 (91%)*	
Experience of previous missed SAH “No”	5 (9%)	2 (9%)	3 (9%)*	0.9

†Participants asked if they would accept a higher risk of missed SAH for a quicker, cheaper or less invasive test.
*Question omitted by one consultant, ‡Question omitted by two consultants, ◊Question omitted by three consultants.
LP, Lumbar Puncture

Fewer than 10% of respondents in each group indicated a willingness to substitute the LP in favour of a cheaper or quicker test if it carried an increased risk of missed diagnosis (question 11). However, ED clinicians were more likely to accept an increased risk of misdiagnosis for the benefit of a non-invasive test (38% vs 11%, p = 0.02, see table 4).

Figure 5. Factors reported to influence work up of suspected SAH



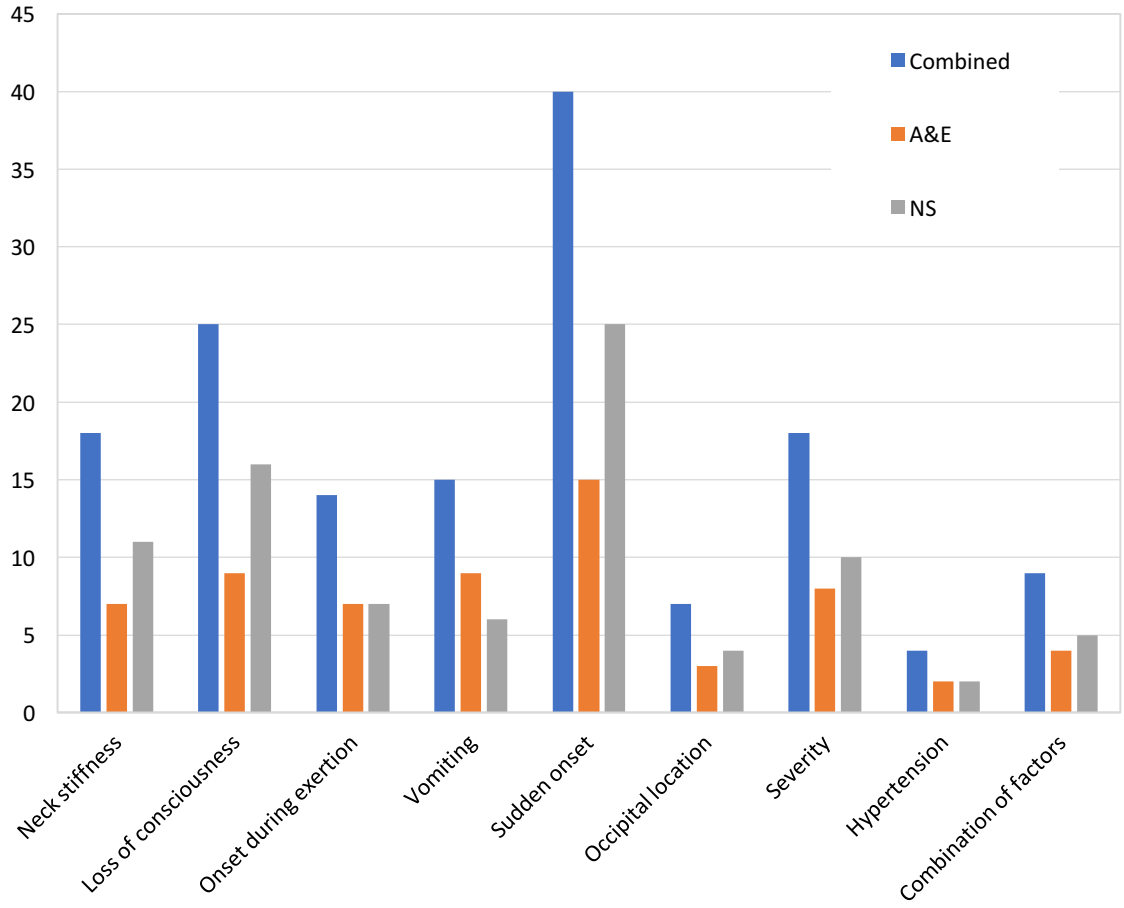
Almost all clinicians in both groups reported direct personal experience of missed SAH due to incomplete investigation (91% in both groups). Fifty-five percent of clinicians had given evidence in a medico-legal capacity and although this was more common amongst ED clinicians (65% vs 51%), the difference was not statistically significant (question 14).

Overall, 22% of clinicians reported that they would feel obliged to investigate SAH if it had been raised and documented as a potential diagnosis, irrespective of their own clinical judgement (question 2). There was no significant difference between ED clinicians and neuro-specialists in this regard.

Clinicians indicated clinical characteristics which would mandate investigation for suspected SAH in their own personal practice (see appendix 2, question 1). Of the 58 responses to this question, 12 were excluded because they were self-contradictory. Of the remaining 46 consultants, “sudden onset headache” was the

clinical feature most commonly reported to mandate investigation for possible SAH. Other clinical features which determined further investigation are illustrated in Figure 6.

Figure 6. Clinical features mandating investigation for SAH



Some clinicians also indicated that certain clinical factors would stop them pursuing a diagnosis of SAH. Absence of “high risk features” on clinical review was the most commonly cited reason to stop investigating possible SAH (see figure 7, question 3). Eight consultants reported that resolution of the headache would persuade them to stop investigations for suspected SAH (15% of all respondents).

Figure 7. Factors preventing further investigation of SAH.

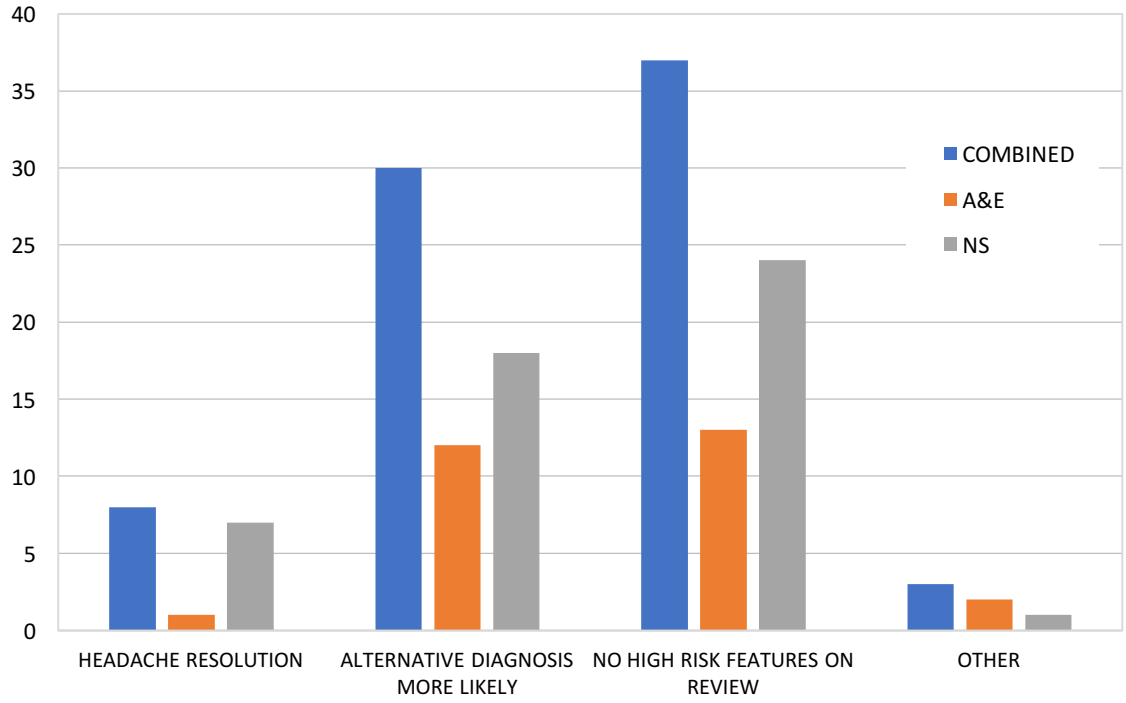
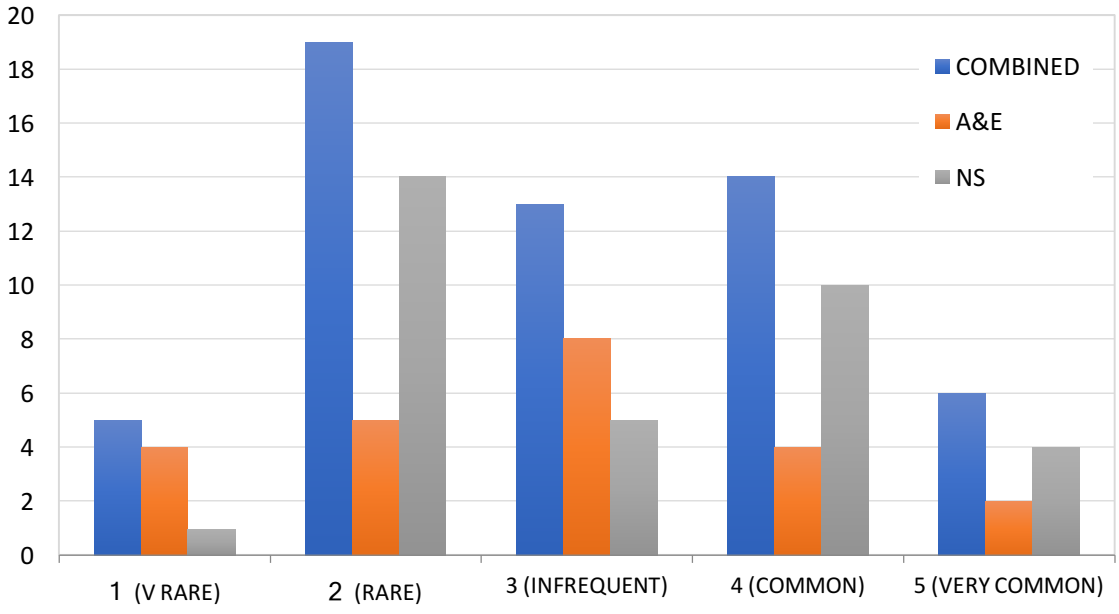


Figure 8. Clinicians' estimated frequency of lumbar puncture complications. Ordinal scale provided: Very rare is <1 in 200; Rare ~1 in 500; Infrequent ~1 in 200; Common ~1 in 100; Very common ~1 in 20.



Although free text answers were not requested from participants some responses were annotated. Where relevant, these are discussed below.

Although SAH is a relatively rare disease, its misdiagnosis was a familiar experience for more than 90% of consultants. The consequence of missed diagnosis can be devastating for patients and carries significant medico-legal implications for doctors and healthcare institutions. It is therefore difficult to understand the frequency with which clinicians stray from recommended practice, especially considering the defensive nature of modern medicine (Anderson 1999).

There is an extensive body of published research evaluating the appropriateness of different strategies for SAH diagnosis. Whilst there remains controversy regarding the utility of LP in the diagnostic pathway, all national and international guidelines currently recommend the procedure for patients with negative initial imaging. A recent survey of UK Emergency and Acute medicine clinicians confirms a wide variation in practice with only 74% of respondents following the recommended CT-LP pathway (Dobb and Cooper 2013).

This is the first study to investigate whether clinicians' risk-tolerance might account for the observed variation in practice and to survey clinicians' appraisals of the relevant recommendations explicitly.

Almost all respondents had a personal experience of missed SAH diagnosis, however only 70% agreed with the guidelines that LP was mandatory for all CT negative cases. Whilst 88% of neuro-specialists agreed with the guideline, only 39% of ED physicians held this view. Furthermore, ED specialists accepted a higher risk of missed diagnosis compared to neuro-specialists when investigating suspected SAH.

Previous attempts to explain deviation from guidelines have suggested lack of awareness as a possible cause. Taken together, our findings suggest that clinicians are well aware of the perils of missed diagnosis, but are nevertheless sceptical of the benefits of LP in the diagnostic pathway. Furthermore, there appears to be a significant difference in opinion across the groups studied. Although local practices and policies were influential in deciding work-up of SAH, personal experience was the most commonly cited factor by clinicians.

The LP is often considered a gold standard test in the literature. To avoid any misconceptions about LP accuracy respondents were asked to assume that LP had an imperfect sensitivity when considering whether or not it should be performed routinely in CT negative cases (question 8). This question is similar to a preceding question which asks respondents whether or not they endorse the guideline stipulation that “LP should be mandatory in all CT negative cases”. Whilst ED physicians were consistent in their answers to both questions there was a 14% swing in the responses of the neuro-specialist group. The number of neuro-specialists endorsing the routine use of LP reduced when asked to assume its sensitivity was imperfect. This suggests that a proportion of the neuro-specialist respondents believe that the LP has perfect sensitivity.

It is typically the emergency and acute medical physicians who are compelled to perform an LP before referring or discharging patients with suspected SAH. Neuro-specialists are more likely to be involved in an advisory capacity until a diagnosis has been made. The LP may therefore serve as a filter, reducing unnecessary referral to specialist services (Ditta, Galea et al. 2013). ED consultants were more willing to trade off benefits of a non-invasive diagnostic test against the increased risk of missed diagnosis. Neuro-specialists did not tend to share this view which may reflect a concern that referrals would increase if alternative tests were more readily performed.

This survey was not designed to test clinicians’ knowledge of guidelines, epidemiology of SAH, or the performance of diagnostic tests. Nevertheless, some responses did indicate common misconceptions. For example, although the LP is taken as a gold standard test, its sensitivity in CT negative SAH is difficult to reliably calculate due to empirical limitations outlined previously.

Application of the most reliable method of spectrophotometric CSF analysis incurs a large number of equivocal results with more than 15% of LP results inconclusive according to Clinical Biochemistry Guidelines (Cruickshank, Auld et al. 2008, Sayer, Bloom et al. 2015).

Recent research has suggested that CT approaches 100% sensitivity in acute SAH if performed within six hours of ictus. This has led to calls for a change of

practice to forego the LP in patients scanned for suspected SAH within 6 hours of the onset of headache (Backes, Rinkel et al. 2012, Edlow and Fisher 2012, Blok, Rinkel et al. 2015, Rinkel 2016). Participants were specifically asked about this scenario (question 4b). ED clinicians were more willing to adopt this policy than their neuro-specialist counterparts, which may reflect a desire to reduce pressure on emergency departments.

The concept of safe discharge has been deemed “irrational, unhelpful and unachievable” because it raises unrealistic expectations of a risk free environment (Goodacre 2006). Conversely, accepting an arbitrary threshold for risk may seem callous or even negligent as it consigns some patients to an adverse outcome (O'Keeffe 2015). Interestingly, five neuro-specialists stated that they would only stop investigations for SAH when the risk of missed diagnosis was reduced to zero. None of the ED consultants shared this view. ED clinicians accepted a higher risk of missed diagnosis compared to their neuro-specialist counterparts. Their reluctance to resort to LP may also reflect a greater tolerance of risk in this group.

It is arguably inappropriate - for patients and health services - that a medical intervention should be determined entirely by the risk threshold of an individual doctor (O'Keeffe 2015). However, it is equally undesirable for guidelines to impose an arbitrary risk threshold that is based on opinion rather than evidence. To be accepted by clinicians and patients, guidelines may need to accommodate a range of possible risk preferences. This could apply to a variety of clinical situations - involving different specialities and health care systems - where there is a fine balance between clinical risk and benefit.

Our findings show that a majority of ED clinicians believe the LP should not be considered a mandatory test following a negative CT. Furthermore, most clinicians indicated a tolerance for missed diagnosis of SAH distinct from the guidelines which afford no misses (Pines and Szyld 2007). ED clinicians’ tolerance of missed SAH diagnosis was almost three times higher than their neurospecialist colleagues. This indicates that the current guidelines do not closely reflect ED clinicians’ risk tolerance for SAH investigation - despite the fact that it is this group who usually manage patients presenting with the acute

sudden onset headache. Incidentally, the Royal College of Emergency Medicine was not represented in the formulation of the current RCP Stroke guidelines (confirmed by personal correspondence).

Limitations

The lack of an appropriate instrument to measure clinicians' risk tolerance necessitated the development of a novel questionnaire. Despite our best efforts, the responses indicated some shortcomings of this tool that limit the strength of the data. Seven respondents were believed to have misinterpreted questions because the answers they provided were incompatible with the question asked. Although these responses could be excluded from the final analysis, other misrepresentative responses may exist within the dataset. The development and validation of an instrument to reliably measure risk tolerance was outside the scope of this study. Although we did not feel the lack of such a tool precluded investigation, our findings require cautious interpretation as a result.

A targeted approach to recruitment (by e-mail, telephone, or in person) was adopted to optimise participation. However, this may have introduced a degree of bias since not all respondents were contacted in exactly the same manner or at the same time. An online survey may have generated more responses and would have been easier to conduct at a national level but would not have overcome participation bias. We felt a targeted pilot survey was an appropriate starting point that could be used to inform future study.

The survey is limited by a poor response rate, which introduces the possibility of participation bias. Although response rates were similar between the two groups, different factors may have influenced each group. Response rates were not balanced across institutions (ranging between 17% and 42%) and as such our results are skewed towards the NHS Trust that provided the most responses.

The questionnaire used in this survey did not differentiate between spontaneous SAH in general and aneurysmal SAH. As such it could be argued that the definition was ambiguous with some clinicians answering in reference to aneurysmal SAH and others considering all causes of spontaneous SAH of which aneurysms are responsible for 85% of cases. However, as previously discussed

no test is able to reliably define aneurysmal SAH. The questionnaire referred to "*SAH in the well patient i.e. an alert, neurologically intact adult presenting with a non-traumatic, sudden, severe headache*" thereby including aneurysmal SAH as a potential cause. In practice, the LP is used as a tool to exclude SAH as a cause of a patient's headache rather than make the diagnosis of aneurysmal SAH which requires investigation for an underlying vascular lesion. It was therefore felt to be reasonable to simply refer to SAH rather than mention an underlying aneurysmal cause.

As with any survey of this type, hypothetical scenarios can never accurately reflect real-life practice. This problem is amplified when considering abstract concepts such as risk. We asked respondents to quantify their acceptable risk of a missed diagnosis which is a particularly challenging task - reflected in the fact that 4 of the 58 respondents did not provide an answer to this question. Even though a vignette was used to provide a clinical context, clinicians may have felt uncomfortable being asked to characterise their acceptance of risk using a statistical probability. However, this is a common scenario faced by clinicians in their daily practice when patients ask them to quantify the chance of complications from an invasive procedure, diagnostic test, or surgery. Furthermore, incorporating relevant quantitative research findings into clinical decision-making is the very basis of evidence-based medicine. Therefore, although a simulation, the scenario presented to clinicians is a realistic challenge, similar to that commonly faced in the healthcare setting.

One respondent indicated that they would ask the patient to determine their own level of acceptable risk rather than assume this responsibility for themselves. It is possible that other participants shared a similar view and felt our question was incompatible with their own professional approach. This raises interesting questions about the doctor-patient relationship, the didactic nature of guidelines, and the role of patients in guideline development. Clinical risks need to be acceptable to patients first and foremost and patient-centredness has become a dominant paradigm in modern medicine (van de Bovenkamp and Trappenburg 2009). However, transferring responsibility to patients can only lead to empowerment if they are supported in the decision-making process and the best evidence is made easily accessible to them.

Patient participation is encouraged in guideline development (NICE 2015) on the assumption that active patient involvement will enhance the quality of guidelines. However, it has been argued that this mechanism is ill suited to achieving patient-centred care at the individual level. As described by van de Bovenkamp and Trappenburg (2009) training and supporting patients to participate as full members in guideline development is a double-edged sword. Patients who have been adequately trained and supported become fellow academics and may no longer be able to contribute the experiential knowledge for which they were asked to participate in the first place. Patients who were not properly trained do contribute experiential knowledge, but studies have shown that it is difficult to incorporate this in evidence based guidelines.

Clinicians continue to play a key role in guiding patients through complex medical decisions. Although challenging, further study of clinicians' risk-benefit appraisals could improve our understanding of clinical behaviours and ensure that guidelines and doctors work together to deliver patient-centred care.

Conclusion

This survey provides a possible explanation for the observed variation in practice of SAH investigation. Opinions vary significantly between ED clinicians and neuro-specialists with respect to the utility of LP and their tolerances for the risk of missed diagnosis. Omission of the LP from the diagnostic work-up may reflect scepticism about its utility rather than an unawareness of the risk of missed diagnosis.

The survey findings indicate that for some clinicians, a non-invasive alternative to LP would be a desirable tool for SAH diagnosis even if this came at the expense of reduced sensitivity. It is therefore appropriate to pursue a study evaluating the diagnostic performance of a non-invasive test as a potential alternative to the LP. To be of clinical utility this test need not demonstrate superiority to the LP, but it would need to demonstrate added value over and above CT.

The preliminary parts of this thesis demonstrate that such a test may achieve clinical utility by virtue of its ability to deliver comparable outcomes in a simpler way.

Part III: IMAGING PROJECT

Introduction

CT is a highly sensitive first line diagnostic test for SAH, especially if used soon after symptom onset (Perry, Stiell et al. 2011). However, its imperfect sensitivity and the severe consequences of missed diagnosis are such that guidelines recommend the use of an invasive test (the lumbar puncture) in cases where initial imaging is negative.

The sensitivity of CT to detect SAH reduces with time. Studies looking at the ability of MRI to detect SAH compared to CT have indicated a potential role for MRI in the diagnosis of SAH where presentation is delayed. Verma, Kottke et al. (2013) found an enhanced sensitivity of combined SWI and FLAIR sequences compared to CT in a retrospective review of patients imaged following SAH. This study included patients with various aetiologies of SAH (traumatic, aneurysmal, AVM rupture) and compared the detection of regional SAH identified using the different imaging techniques. There was an average delay of 54 hours between symptom onset and acquisition of MRI scans in this study. In addition, there was a significant delay between CT and MRI (mean of 48 hours). Redistribution of blood around the subarachnoid space could have influenced their findings, rather than there being a true difference in the sensitivity of imaging to detect haemorrhage. Hodel, Aboukais et al. (2015) performed a similar study utilising 3D FLAIR, DIR and SWI imaging. The prospective nature of this study allowed better control over scan timings with the delay between CT imaging and MRI limited to just 3 hours (range 2 – 5 hours). All patients in this study had spontaneous SAH however, there was a significant delay between symptom onset and MRI acquisition (14 to 16 days). In addition, these patients had a degree of neurological impairment as indicated by a reduced score on the Glasgow Coma Scale (average 14.1; range 10-15).

MRI has potential utility as a diagnostic test for SAH in the acute clinical setting – performed as soon as possible after presentation to hospital on neurologically intact patients with an acute onset of headache who are suspected of SAH. To date no study has compared the performance of MRI and CT in this group of patients, or in this timeframe.

Aim

To establish whether FLAIR, DIR and SWI imaging is better able to detect regional SAH than CT in neurologically intact individuals presenting with thunderclap headache and confirmed SAH.

Method

Patients

Patients were recruited if they presented with a sudden onset headache suspicious for acute spontaneous SAH, had no history of recent head injury and no history of neurological or neurosurgical disease. Only those patients with intact neurology and GCS of 15 were eligible for inclusion.

Inclusion Criteria

- A signed and dated, informed consent obtained prior to study participation
- Aged between 18 - 90 years
- CT scan demonstrating SAH
  OR
- LP positive for xanthochromia by photospectrometry - performed between 12 hrs and 14 days of symptom onset (following negative CT scan)
- No falls or direct trauma to the head in the previous 7 days
- Access to MR within 6 hrs of a positive CT
- Able to tolerate MRI and safe to scan following standardised MRI safety questionnaire
- GCS 15

Exclusion Criteria

- Age < 18 or > 90 years.
- History of neurological / neurosurgical disease / major head injury
- Previous diagnosis of intracranial haemorrhage or brain neoplasm
- Focal neurological deficit and / or GCS < 15

Consented participants underwent a dedicated SAH protocol MRI scan on 1.5T scanner systems (Siemens Avanto, software package VB17). Scanner parameters varied slightly due to local optimisation processes as outlined below. MRI is not part of the normal clinical diagnostic pathway in any of the centres of this study.

- 3D FLAIR
  Charing Cross Hospital (TE: 328; TR: 6,000; IT: 2,200; Flip angle 120; slice thickness 3mm; matrix: 194x256; FoV: 174x230)
  Royal London Hospital (TE: 401; TR: 4,800; IT: 1,600; Flip angle 120; slice thickness 1mm; matrix: 256x258; FoV: 256x256
- Axial 2D FLAIR
  Charing Cross Hospital (TE: 109; TR: 9,000; IT: 2,500; Flip angle 150; slice thickness 5mm; spacing 5.5 mm; matrix: 256x256; FoV 250x250)
  Royal London Hospital (TE: 97; TR: 9,000; IT: 2,499; Flip angle 150; slice thickness 5mm; spacing 5.5 mm; matrix: 320x210; FoV 210x240
- SWI
  Charing Cross Hospital (TE: 40; TR: 49; Flip angle 15; slice thickness 2mm; matrix: 177x256 FoV: 201x230)
  Royal London Hospital (TE: 40; TR: 48; Flip angle 15; slice thickness 1.5mm; matrix: 195x320 FoV: 186x230)
- DIR
  Charing Cross Hospital (TE: 327; TR: 7,500; IT: 3,000; Flip angle 120; slice thickness 1.5mm; matrix: 192x192; FoV: 280x280)
  Royal London Hospital (TE: 308; TR: 7,500; IT: 3,000; Flip angle 120; slice thickness 1.5mm; matrix: 192x192; FoV: 280x280)

For logistical reasons one patient's DIR was scanned on a 3T system (Siemens Verio, software package MR B17; TE: 308; TR: 7,400; IT: 3,000; Flip angle: 120; slice thickness: 1.29mm; matrix:192x192; FoV: 249x249)

CT

As part of routine clinical care patients underwent CT at Charing Cross Hospital and Royal London Hospital.

Charing Cross Hospital
Siemens Somatom Definition AS+
Slice Thickness: 7.2mm Cerebrum; 2.4mm Cerebellum
kVp: 120, Focal spot 1.2 mm, 512 x 512 matrix

Royal London Hospital
Siemens Somatom Definition AS+
Slice Thickness: 1mm (whole head)
kVp: 120, Focal spot: 1.2 mm, 512 x 649 matrix.

Image interpretation

Image interpretation was performed separately by two experienced neuroradiologists (JL and PB) using a standardised template to score regional SAH on CT and MRI sequences. CT and MRI scans were scored independently. Cross referencing between MRI modalities was permissible but cross referencing between MRI and CT was avoided so that diagnostic information available on MRI did not influence the interpretation of the CT and vice versa. Any disagreement between readers was reviewed at a consensus reading.

Regions of subarachnoid haemorrhage were scored according to a 3-point scale where 0 denotes normal (no haemorrhage), 1 denotes an equivocal finding and 2 denotes an unequivocal positive finding. A finding was deemed equivocal if the contrast resolution was limited relative to background noise, and/or when artefact obscured the region in question (e.g. pulsation artefact or susceptibility artefact in MRI or beam hardening artefact in CT). Regions that were scored as equivocal were taken to be negative for the purposes of subsequent analysis.

A combination of standard images, MIP and phase images were used for SWI interpretation. SAH was rated unequivocal when a non-structurally referenceable hypointense signal alteration was detected in the cisterns, sulci or ventricles, surrounded by isointense parenchymal or CSF signal intensity in the subarachnoid space. As described by Wu, Li et al. (2010), SAH was differentiated from veins running in the sulci by assessing their shape (i.e. veins are regular, smooth and uniform compared to areas of SAH which appear as irregular and

non-uniform with a rough boundary and a slightly triangular form). If haemorrhage was suspected, the neighbouring sections are also evaluated to confirm SAH.

Regional classification

Regional classification of SAH was appraised using the methodology described by Wu, Li et al. (2010) with the minor modification that, where possible, subarachnoid regions were separated by their lateralisation (i.e. “Sylvain fissure” was subdivided into both left and right Sylvain fissures).

The subarachnoid compartment is therefore divided into 14 regions as follows:

Convexity subarachnoid spaces:

(1) LEFT frontal-parietal

(2) RIGHT frontal-parietal

(3) LEFT temporal-occipital

(4) RIGHT temporal-occipital

(5) interhemispheric fissure;

Cisternal subarachnoid spaces:

(6) LEFT Sylvian cistern

(7) RIGHT Sylvian cistern

(8) perimesencephalic cisterns (combination of mesencephalic cisterns and basal cisterns)

(9) posterior fossa cisterns

(10) superior cerebellar cistern (which belongs to the posterior fossa cisterns, but is evaluated separately).

Intraventricular spaces: sub-grouped into

(11) LEFT lateral ventricle

(12) RIGHT lateral ventricle

(13) III ventricle

(14) IV ventricle

Regulatory, ethical and legal issues

Initial Approval

Prior to enrolment of subjects, the Independent Ethics Committee (IEC) provided written approval of the conduct of the study at named sites and reviewed the

protocol, patient information sheet (PIS) and the informed consent form (ICF) provided to the subjects. Local Trust approval was also obtained prior to study commencement.

Consent

Informed consent to enter the study was sought from each participant after a full explanation of the study. An information leaflet was provided and time allowed for consideration. Potential participants were told they could refuse or withdraw from the study at any time without the need to give any reason and without prejudicing further clinical care.

Recruitment

Recruitment of 12 patients was planned based on statistical considerations for a pilot study described elsewhere (Steven 2005). Successful recruitment of five patients was achieved within four months of the study opening at Charing Cross Hospital (CCH) in April 2014. After this time, the primary author left CCH as part of a rotational neuroradiology training programme. In an attempt to continue recruitment, the author extended the recruitment period at CCH and attempted to set up an additional study site at University College London Hospital (UCLH) to allow study completion. Despite ethical approval, availability of scanner time and installation of required sequences prevented active recruitment at this site. A final attempt was made to complete recruitment following the author's substantive appointment to Barts Health NHS Trust as a Consultant Neuroradiologist. Unfortunately, local practices at the Royal London Hospital (RLH) prevented most external SAH referrals from being eligible for study inclusion thereby severely limiting the likelihood of completing recruitment. One further patient was recruited at RLH before recruitment window closed on in March 2019. It was deemed not viable to extend the study beyond this time.

Analysis

Relative locational sensitivity

Relative locational sensitivity for 2D FLAIR, 3D FLAIR, DIR and SWI and CT was calculated according to the methodology described by (Mitchell, Wilkinson et al. 2001). The presence or absence of blood in a location on any of the MR sequences or CT was assumed to be the "ground truth". The proportion of

regions in which haemorrhage was detected for a specific modality then serves as the relative locational sensitivity. For example, if haemorrhage is detected in a total of 20 regions in the sample and CT was only positive in 10 of these regions, then the relative locational sensitivity would be calculated as 50% for CT.

Secondary analysis

Subgroup comparison of regions detected across individual MRI sequences and modalities – e.g. SWI versus CT and FLAIR versus CT, 2D FLAIR vs 3D FLIAR etc.

Results

SAH detection by CT and different MRI sequences

A cohort of 6 patients (3 men, 3 women) were enrolled into the study with an average age of 53. Five patients had SAH diagnosed on CT and one patient had SAH diagnosed based on a xanthochromic LP performed at an external hospital prior to transfer to the study centre. This patient was included in the study despite the fact that the CT and MRI scans was performed outside a 6 hrs window because there was no blood evident on CT, therefore any region of haemorrhage detected on MRI could have been attributable to increased sensitivity. The method and criteria for xanthochromia definition at the external hospital was not indicated in the clinical notes, however when contacted the laboratory confirmed that they routinely perform spectrophotometric assessment for bilirubin according to the latest guidelines.

The average delay between positive CT scans and MRI was 111 minutes. The average time from symptom onset to CT was 29 hrs - this includes one patient in whom SAH was diagnosed on spectrophotometry from an external hospital. In this patient CT and CTA was performed as part of her normal diagnostic work up 52.5 hours after ictus. This patient also had a CT externally which was reported as normal.

Five patients were scanned at Charing Cross Hospital during the initial study recruitment period. The study was subsequently opened at Barts Health where a further patient was scanned. The scanner systems were the same at Barts and Charing Cross (1.5T Siemens Avanto running software VB17) with the exception

of one DIR sequence which was which had to be performed on a 3T system (Siemens, Veria, software VB17) for logistical reasons. The sequences were the same across scanners but variations in scan parameters did exist due to different sequence optimisation processes undertaken by both institutions as described previously.

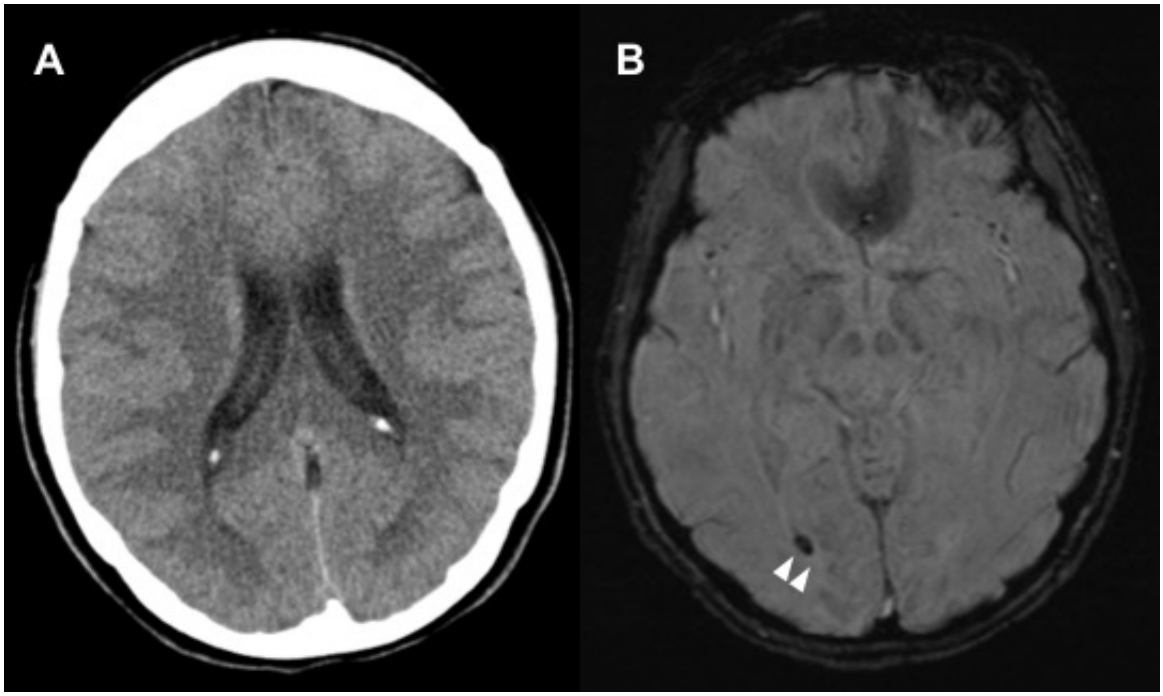
Following independent scan reading there was a 73% inter-rater agreement (115 disagreements out of 420 regions of interest). When all equivocal classifications were removed (with equivocal responses categorised as negative) the inter-rater agreement was 83%. Consensus read was then undertaken to yield the final dataset (see Appendix 3).

Sixty-one regions of haemorrhage were detected out of a possible total of 84. Relative regional sensitivities were calculated assuming that each positive region of haemorrhage represented a true positive finding. CT was negative in 45 of the 61 regions where haemorrhage was detected by an alternative MRI sequence. Table 5 provides a break-down of regional sensitivity scores for each modality / sequence and figures 9 and 10 provide imaging examples.

Table 5. Regional sensitivity of imaging modalities

Modality/Sequence	Number of regions positive for SAH	Instances of SAH detected solely by modality/sequence
CT	23 (38%)	0
2D FLAIR	45 (74%)	0
3D FLAIR	53 (87%)	1
DIR	54 (89%)	2
SWI	33 (54%)	4

Figure 9. Intraventricular blood not seen on CT (A), but seen on SWI (arrowheads in B)

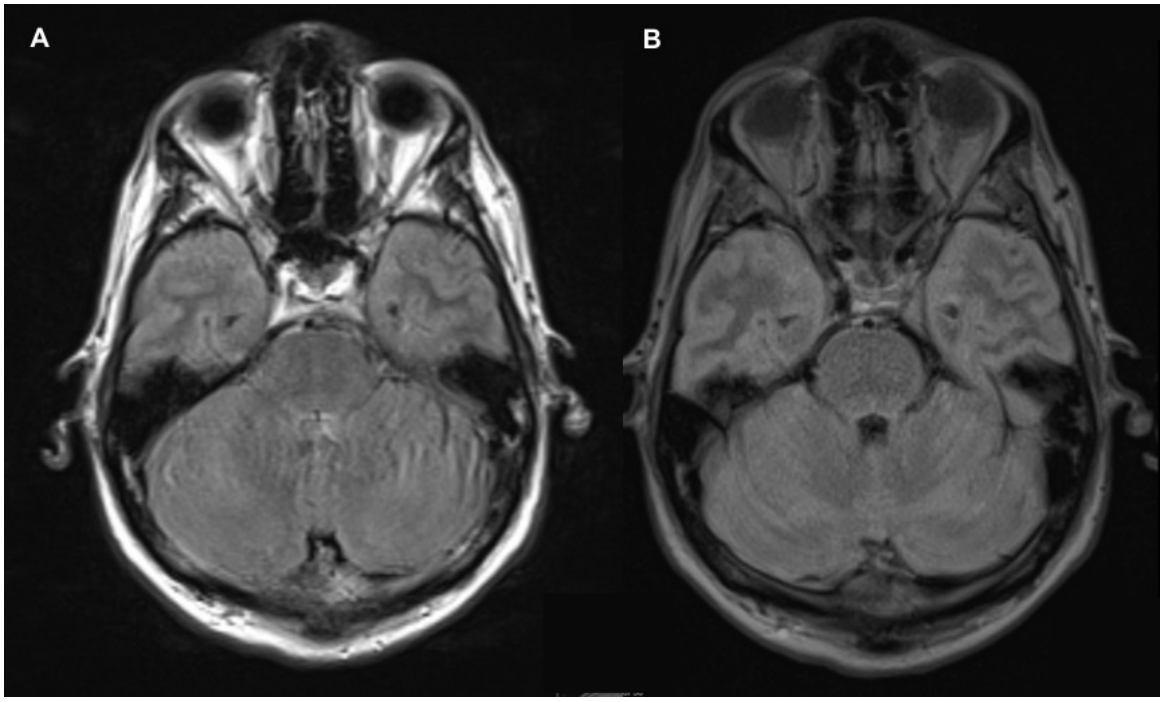


There was no example of CT detecting haemorrhage which was occult on MR imaging. Conversely, regional haemorrhage was detected solely on the basis of DIR on 2 occasions (1 x interhemispheric SAH and 1 x Sylvian fissure), and SWI on 4 occasions (all intraventricular SAH).

Compared to the 3D FLAIR sequence, 2D FLAIR imaging was unable to unequivocally detect haemorrhage on 11/53 of instances. This was most often due to pulsation artefact obscuring the region of interest (see figure 10). Surprisingly, the 2D FLAIR proved superior to the 3D FLAIR on 2/56 occasions due to greater contrast resolution relative to the 3D sequence. In each of these instances haemorrhage was also detected by at least one other sequence (DIR or DIR and SWI).

Given the exploratory nature of this pilot study it was not possible to perform a power calculation and the small sample size means that it is not possible to generate meaningful measures of the statistical probability underlying the observations.

Figure 10. 2D FLAIR image (A), demonstrating pulsation artefact which obscures the posterior fossa. High signal in the 4th ventricle is artefactual and could mask real haemorrhage but is clearly seen on the 3D FLAIR sequence and appears normal. High signal in the pre-pontine cistern is seen on 2D and 3D sequences and is genuine SAH.



Discussion

In this sample of patients presenting acutely with subarachnoid haemorrhage, a dedicated SAH protocol comprising 3D FLAIR, DIR and SWI pulse sequences detected more regions of haemorrhage than CT. More often than not, CT was unable to detect haemorrhage in regions implicated by one or more of the dedicated SAH protocol pulse sequences. The time control between CT and MRI (less than two hours on average) means that the observed difference is unlikely to be due to blood redistribution between scans.

It is theoretically possible that patients suffered a re-bleed in the interval between CT and MRI but there was no clinical deterioration in this short interval in any case to suggest this. Furthermore, when viewed on a case by case basis, every patient with a positive CT scan had at least one instance of regional

haemorrhage detected on MRI but not evident on CT. The likelihood that every patient suffered a re-bleed to account for the observations, and that this occurred within the average 111 minute interval between scans, without any clinical deterioration, can be considered negligible.

In no case was acute SAH detection with CT superior to MRI whereas MRI consistently outperformed CT in terms of regional sensitivity.

The 3D FLAIR acquisition on the current study provides excellent CSF pulsation suppression and allows confident diagnosis of haemorrhage in regions which may have otherwise been deemed equivocal because of the presence of artefact (see figure 10). A standard 2D FLAIR sequence was unable to detect haemorrhage on 11/56 of instances compared to the 3D FLAIR sequence. An unexpected finding was that 2D FLAIR surpassed 3D FLAIR in two instances, however in both cases another sequence in the MR protocol was able to detect the haemorrhage. Therefore, exclusion of 2D FLAIR from the protocol would not have had a negative impact on the combined sensitivity of the MRI protocol in the cohort.

This study was not designed to compare the diagnostic accuracy of MRI with LP. However, one case of CT negative LP positive SAH was included and underwent an MRI almost 27 hours after symptom onset. SWI, which performs well in the subacute period failed to demonstrate haemorrhage in this case (Patient 3 in appendix).

Mohamed, Heasly et al. (2004) performed a retrospective review of CT negative SAH cases at their institution and showed that subsequent MRI examinations revealed SAH in 2 of 12 cases using the FLAIR sequence. They conclude that the large proportion of false negative FLAIR scans (10 out of 12) make the sequence inappropriate as a replacement for LP in SAH diagnosis. However, their study has a number of limitations which are overcome by our design.

Firstly, their method of CSF analysis required detection of red blood cells in the CSF and may have resulted in false positive LPs being interpreted as true positive findings. To avoid this, our study utilised cases of SAH confirmed on CT.

Where a diagnosis of SAH was made by LP this was based on bilirubin detection as defined by UK guidelines which avoids false positive results caused by the presence of oxyhaemoglobin.

Secondly, the retrospective design of the Mohamed study meant that the MRI-CT interval was not closely controlled with MRIs performed up to 7 days after the CT/LP. This means that the detection of haemorrhage on MRI could be due to repeat or redistributed haemorrhage rather than improved sensitivity of the modality itself. Our prospective design is the first to indicate superiority of MRI above CT in the detection of acute subarachnoid haemorrhage when the comparison is made within a tightly controlled time period.

A further improvement of our study is the use of a dedicated haem-sensitive MRI protocol which is optimised to detect acute haemorrhage (using 3D FLAIR, DIR sequences) and subacute / chronic haemorrhage (SWI).

Our findings indicate that a dedicated SAH protocol could detect acute SAH in cases where a CT is normal. The 6 patients in our cohort had blood distributed in different concentrations throughout their subarachnoid spaces. The concentration threshold for detection of acute SAH on MRI cannot be inferred from the findings in this study but it can be assumed that the differences in relative locational sensitivity observed here are manifestations of the variable ability of each sequence to detect blood at different concentrations.

It can be assumed that there is a concentration threshold below which SAH will not be evident on MRI. It might be argued that this fact means MRI is an inappropriate alternative to LP. However, as previously outlined, spectrophotometry also has a concentration threshold below which SAH will not be detected. Furthermore, the UK guidelines for bilirubin analysis incorporate calculations which further reduce sensitivity of CSF analysis in order to achieve greater specificity.

Limitations

A major limitation of this pilot study is its small sample size. Planned recruitment of 12 patients failed for a number of reasons. Firstly, the disease is relatively rare

and the requirement that patients had no neurological deficit further reduced the number of eligible patients presenting within the study period. The scarcity of patients was compounded by the tight time window required for recruitment (within 6 hours of an abnormal CT) which meant that patients referred into the study site from other hospitals were often ineligible for recruitment unless the CT was repeated for clinical reasons following transfer. Secondly, scans were time critical and unpredictable but had to be scheduled around clinical work-flow within limited the hours of routine service. Patients presenting out of normal working hours could not typically be recruited.

The study is further limited by a number of methodological factors. In an attempt to derive a regional sensitivity measure for SAH detection the subarachnoid space was subdivided into arbitrary regions of uneven size without clearly defined borders. Consequently, there was some disagreement in the radiology readings which reflect the subjective anatomical definitions and required consensus review.

Regions of haemorrhage were defined as equivocal depending on the presence of artefact in the region of interest in an attempt to standardise findings in a more objective way. However, the process remains a rather subjective endeavour. What may be considered artefact by one reader may be judged to be genuine pathology by another reader. Nevertheless, subjectivity is an inseparable part of radiological interpretation and cannot be eradicated entirely. Therefore, although partial to subjectivity, the radiological process followed here (independent reads with consensus review) is reflective of normal practice. Of note, LP-driven SAH diagnosis is not free of this limitation and often relies on the subjective interpretation of spectrophotometric graphs.

Conclusion

This pilot study is the first of its type to prospectively evaluate the ability of a dedicated MRI protocol to detect acute subarachnoid haemorrhage in patients without neurological impairment or reduced GCS. It is this specific cohort of patients who represent a diagnostic challenge for investigation of SAH. Current practice dictates that an LP is routinely performed but this is time consuming, unpleasant for the patient, of variable utility and not without risk of complications.

The lack of a reliable gold standard test for the diagnosis of SAH limits the validity of any measure of sensitivity and specificity – even when large patient cohorts are studied. The relative locational sensitivity measure provided here is not without its own limitations and requires cautious interpretation. Nevertheless, our findings indicate that MRI could add value in the diagnosis of SAH by identifying haemorrhage in cases where CT is negative.

Future directions

These preliminary findings indicate that blood sensitive MRI sequences are complimentary to CT in the detection of aneurysmal SAH.

MRI is not as widely available as CT and is less commonly staffed out of hours: just 12.2% of MRI scanners are run 24/7 according to a recent NCEPOD (2013) investigation compared to 74.5% of hospitals providing a 24/7 LP service. This could limit the feasibility of performing an MRI as a second-line investigation in place of LP. However, CSF samples are often sent to central laboratories for analysis which can delay diagnosis (Martin, Page et al. 2014). Furthermore, the need to delay the LP by at least 12 hours post ictus often prolongs the diagnostic pathway and necessitates costly hospital admission. In these cases, an MRI performed in hours (next day for overnight admissions) could still speed up the diagnostic pathway. Future study could investigate the relative costs, speed and feasibility of adopting the MRI as an alternative to LP.

Recently, vessel wall imaging has been used to demonstrate unstable aneurysms and sites of rupture (Edjlali, Gentric et al. 2014, Nagahata, Nagahata et al. 2016, Wang, Zhu et al. 2018). Spin-echo, spatial presaturation and double inversion recovery MRI techniques can be utilised to supress signal from blood and CSF allowing visualisation of the vessel wall (Mandell, Mossa-Basha et al. 2017). Subsequent administration of an intravenous contrast agent can be used to demonstration vessel wall enhancement which is an abnormal finding. Enhancement of an aneurysm is thought to represent the inflammatory process seen in active, unstable aneurysms. Future study could combine the haem-sensitive protocol outlined here, with MR angiography and vessel wall imaging. Use of cross sectional angiography in the diagnostic pathway has been criticised because it is unable to distinguish incidental aneurysms from ruptured

aneurysms, the treatment of which exposes individuals to unnecessary risk. Vessel wall imaging and blood-sensitive sequences could be used to exclude patients with incidental aneurysms from unnecessary emergency treatment and the associated risks.

The double inversion recovery technique utilised in this study could be further modified to improve sensitivity to SAH. Instead of suppressing white matter and CSF, the DIR sequence could be modified to suppress grey matter and CSF as used recently in multiple sclerosis imaging (Tillema, Weigand et al. 2018). This has not been applied to SAH, but in principle could further enhance the contrast resolution of sulcal SAH thereby improving sensitivity. The DIR sequence used in this study was a Work In Progress (WIP) released by Siemens which did not allow modifications in this manner. More recent software updates allowing this sequence manipulation could prove a fruitful avenue for future research.

Conclusion

Although the LP is often viewed as a gold standard test for SAH, its utility is significantly limited. Stringent CSF analysis criteria have been developed to avoid false positive reports in cases of traumatic LP, but are not universally followed and come at a cost of reduced sensitivity. Some authors have argued that these factors undermine the LP so much that it should be abandoned. Others have shown, using a Bayesian paradigm, that the pre-LP probability of SAH is so low following negative CT that thousands of LPs are required to detect very few SAH cases missed on CT (Coats and Loffhagen 2006, Gee, Dawson et al. 2012). Furthermore, even when a positive LP result is found, this does not necessarily indicate an aneurysmal cause of SAH and does not necessarily confer an improved clinical outcome.

This thesis presents three key findings:

1) Clinical practice in neuroscience centres often differs from guidelines with frequent omission of the LP from the diagnostic work up of patients being investigated for suspected SAH.
2) Clinicians have a variety of opinions about the utility of the LP as a test for SAH which, in part, reflect differences in their tolerance of risk. For many clinicians, a non-invasive alternative to LP would be a desirable tool for SAH diagnosis - even if this came at the expense of reduced sensitivity.
3) Blood-sensitive MRI protocol is able to detect more regions of SAH than CT suggesting that it has a greater sensitivity than CT and could in theory diagnose SAH when a CT appears normal.

When viewed together, these findings indicate that MRI has the potential to be a clinically useful test for aneurysmal SAH and could be acceptable to clinicians as an alternative to lumbar puncture following a normal CT.

Despite its limitations, the LP may still be a useful test in subacute presentations where the sensitivity of CT is low and the clinical suspicion of SAH is high (Coats and Loffhagen 2006). Larger prospective studies are needed to investigate whether haem-sensitive MRI can out-perform the LP in these circumstances. It is unclear whether or not the haem-sensitive sequences would have detected SAH in the CT negative case had it been performed at the time of the LP. However,

the failure to detect SAH in this patient does suggest that there will be a continued role for the LP in SAH diagnosis.

This thesis highlights how subjectivity and opinion influence the decision-making processes in medical diagnostics. Future study of risk tolerance in the clinical setting may enhance our understanding of a range of clinical behaviours including referral patterns and diagnostic test use.

Despite the best intentions of evidence based medicine, it is impossible to eradicate uncertainty entirely. Guidelines are powerful tools to homogenise standards of best medical practice but in cases where evidence is weak or disputed, prescriptive guidelines may be poorly followed. In such circumstances guidelines may need to accommodate different risk tolerance preferences to represent the clinicians and patients they are designed to assist.

Further research of risk tolerances may help deliver personalised medicine which empowers patients and ensures that the care they receive reflects their own assessment of risk and benefit. This will require the development of validated instruments to measure risk-tolerance in patients and clinicians.

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Appendix 1

Table 6. Composition of questionnaire respondents

Site	Number	Age	Number	Specialty	Number
CXH	15 (25.86%)	≤40	18 (31.03%)	A&E	23 (39.66%)
QS/UCLH	18 (31.03%)	41-50	25 (43.10%)	Acute Medicine	0
Kings/ PRUH	9 (15.52%)	51-60	13 (22.41%)	Neurosurgery	11 (18.97%)
Romford	9 (15.52%)	>60	2 (3.45%)	Neurology	15 (25.86%)
St Mary's	7 (12.07%)			Neuroradiology	9 (15.52%)

Table 7. Response rates by institution and specialty

Institution	Responses	Specialty	Responses
Kings	9/54 (16.67%)	**Emergency Department**	23/71 (32.39%)
UCLH	18/47 (38.30%)	**Neurosurgery**	11/19 (57.89%)
Imperial	22/48 (45.83%)	**Neurology**	15/71 (21.13%)
BHRT	9/22 (40.91%)	**Neuroradiology**	9/10 (90.00%)
Overall	58/171 (33.92%)		

Appendix 2

Questionnaire: Investigating Subarachnoid Haemorrhage

This questionnaire is designed to survey different approaches to investigating suspected subarachnoid haemorrhage (SAH) in the well patient i.e. an alert, neurologically intact adult presenting with a non-traumatic, sudden, severe headache.

Clinical practice varies widely and there are no right or wrong answers to the scenarios and questions presented here. If you consent to take part in the survey please answer according to ***how you would act*** *rather than how you feel you should respond.*

Your responses will remain anonymous. Please seal your answer sheet in the envelope provided and leave it in the returns box.

Please complete the following details about your medical background and current post by ticking the appropriate boxes.

POST:

Consultant	☐	**Registrar**	☐	**SHO**	☐

AGE:

<40	☐	**41-50**	☐	**51-60**	☐	**>60**	☐

SPECIALITY:

A & E	☐	**Acute Medicine**	☐	**Neurosurgery**	☐	**Neurology**	☐	**Neuroradiology**	☐

YEARS OF POSTGRADUATE MEDICAL EXPERIENCE:

<15	☐	**15-25**	☐	**>25**	☐

Question 1

Please indicate if any of the following headache characteristics **mandate** investigation for suspected SAH in *your personal practice.*

1 neck stiffness	☐	**6 occipital location**	☐
2 loss of consciousness	☐	**7 severity**	☐
3 onset during exertion	☐	**8 hypertension**	☐
4 vomiting	☐	**9 other**	☐
5 sudden onset *(maximal pain within seconds)*	☐	**10 other**	☐

If no individual feature would prompt you to investigate SAH but a combination of features would, please list the factors you require in combination (e.g. "1, 3 and 7"):

Question 2

Do you feel obliged to investigate for SAH once it has been raised and documented as a potential diagnosis, ***irrespective*** of your own clinical assessment of likelihood?

NO	☐	*Go to Q3*	**YES**	☐	*Go straight to Q4*

Question 3

In a patient admitted for investigation of suspected SAH, what clinical factors would stop you taking your investigations any further?

Resolution of headache	
Alternative diagnosis more likely	
Review of history / examination reveals no "high-risk" headache features	
Other *(please specify)*	

Question 4

Please indicate your agreement with the following statements regarding suspected acute SAH.

a) Lumbar puncture **must** be performed if CT or MRI does not confirm the diagnosis.

AGREE		**DISAGREE**	

b) Lumbar puncture can be omitted if a *negative* CT is performed **within 6 hours** of headache onset.

AGREE		**DISAGREE**	

Question 5

Have you ever encountered a SAH patient who re-presented with a re-bleed having been recently discharged from hospital...

. . . . ***without*** intracranial imaging ***or*** LP workup?	**YES**		**NO**	
. . . . following a negative CT but ***without*** an LP?	**YES**		**NO**	
. . . . following a negative CT ***and*** negative LP?	**YES**		**NO**	

Question 6

What is the lowest pick-up rate you would accept to justify **routinely** performing an LP in patients suspected of having CT negative SAH? (check **one** of the options below)

At least 1 SAH case picked up every 100 LPs performed	
1 SAH case picked up every 101-500 LPs performed	
1 SAH case picked up when > 500 LPs performed	

In other words, for every "x" number of LPs performed one SAH is diagnosed which would have otherwise been missed.

Question 7

In your ***personal view*** how common are significant complications following LP (e.g. severe pain at needle site, low pressure headache, spinal haematoma etc.)?

very rare **<1 in 2000**		**rare** **≈1 in 500**		**infrequent** **≈1 in 200**		**common** **≈1 in 100**		**very common** **≈1 in 20**	

Question 8

Assume LP has **less than 100% sensitivity** for SAH in **CT negative** cases. Do you think this would justify ***routinely*** performing an LP following a normal CT head result?

YES		NO	

Question 9

You suspect SAH in a patient who presents within hours of their headache onset. An urgent CT is performed and is normal. Would any of the following factors influence your decision to perform / recommend an LP?

Time constraints (e.g. need to admit / wait up to 12 hrs)	**YES**		**NO**	
Invasiveness of the procedure	**YES**		**NO**	
Reliability of the procedure	**YES**		**NO**	
Cost of the procedure (lab cost, materials, hospital bed)	**YES**		**NO**	

Question 10

Assume a pre-test probability of SAH of 10% in an otherwise well, 40-year-old adult, presenting with a worst-ever "thunderclap headache". What post-test probability would you need to reach before stopping further investigation for possible SAH?

When risk is reduced to ____ % **chance of SAH.**

If you deem the pre-test probability of SAH (10%) acceptably low please tick here: ☐

Question 11

Would you accept a higher risk of missed SAH in the following scenarios?

Non-invasive test (e.g. MRI)	**YES**		**NO**	
Quicker test?	**YES**		**NO**	
Cheaper test?	**YES**		**NO**	

Other (please specify)

Question 12

Assuming a high clinical suspicion of spontaneous SAH, please indicate which of the following tests you would perform before discharging a patient. Assume that each test you perform comes back negative.
Rank only the tests you would use and in the order you would do them (1 = first test; 2 = second etc.)

CT (performed within 12 hours)	
LP (photospectrometry for bilirubin / oxyhaemaglobin)	
LP (visual xanthochromia assessment)	
CTA	
MRI	
MRA	
DSA	
Repeat DSA (please specify preferred time from ictus)	

If you have an alternative preferred diagnostic work-up please indicate here :

Question 13

Which of the following do you feel most strongly influences your work-up of possible SAH? (Please indicate ***all*** that apply.)

Personal anecdotal experience	
Adoption of practices during training	
Formal teaching / lectures	
Local practice / policy	
Resource availability (bed availability etc)	
Other (please specify)	

Question 14

Have you ever been called to give evidence at any type of legal hearing (e.g. coroner's court) in your capacity as a doctor?

YES		**NO**	

Appendix 3

		Region of interest													
		Convexity subarachnoid spaces					Cisternal subarachnoid spaces					Intraventricular space			
		RIGHT		LEFT		Not lateralised	RIGHT	LEFT	Not lateralised			RIGHT	LEFT	Not lateralised	
Patient ID	Modality / Se	frontal-parietal		frontal-parietal		interhemispheric	Sylvian fissure		Perimesencephalic	Post Fossa	Sup Cerebellar	Lateral ventricle		III	IV
1	CT	2	2	2	0	2	2	0	0	0	0	0	0	0	0
1	2D FLAIR	2	2	2	2	2	2	2	1	0	2	0	0	1	1
1	3D FLAIR	2	2	2	2	2	2	2	2	1	2	1	1	0	0
1	DIR	2	2	2	2	2	2	2	2	0	1	1	1	1	0
1	SWI	2	2	2	1	1	2	2	1	0	2	2	2	0	0
2	CT	2	2	2	1	0	0	0	0	0	0	0	0	0	0
2	2D FLAIR	2	2	2	2	1	2	2	1	1	0	1	1	0	1
2	3D FLAIR	2	2	2	2	2	2	2	2	2	2	2	2	0	0
2	DIR	2	2	2	2	2	2	2	2	2	1	2	2	0	0
2	SWI	2	2	2	0	2	1	1	0	0	0	2	2	0	0
3	CT	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	2D FLAIR	0	0	0	0	0	0	0	1	1	0	0	0	0	1
3	3D FLAIR	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	DIR	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	SWI	0	0	0	0	0	0	1	1	1	1	0	0	0	0
4	CT	0	1	2	0	2	1	0	2	2	2	2	0	0	0
4	2D FLAIR	1	2	2	2	2	2	1	2	2	2	2	2	1	1
4	3D FLAIR	2	2	2	2	2	2	1	2	2	2	2	2	1	0
4	DIR	2	2	2	2	2	2	2	2	2	2	2	2	1	0
4	SWI	0	0	0	0	0	0	0	2	2	0	2	2	0	0
5	CT	0	0	0	0	0	0	2	2	2	0	0	0	0	0
5	2D FLAIR	2	2	2	2	0	2	2	2	2	1	0	2	0	2
5	3D FLAIR	2	2	2	2	0	2	2	2	2	2	2	2	0	0
5	DIR	2	2	2	2	2	2	2	2	2	2	2	2	0	0
5	SWI	0	0	0	0	0	0	2	1	0	0	2	2	0	2
6	CT	2	0	0	0	2	2	2	2	1	0	1	1	0	2
6	2D FLAIR	2	2	2	2	2	2	2	2	2	2	0	1	0	2
6	3D FLAIR	2	2	2	1	2	2	2	2	2	2	0	1	0	2
6	DIR	2	2	2	2	2	2	2	2	2	2	1	0	0	2
6	SWI	2	1	2	1	2	2	2	2	2	2	2	2	0	2