SHORT REPORT

Location characteristics of early perihematoma oedema

M O McCarron, P McCarron, M J Alberts

J Neurol Neurosurg Psychiatry 2006;**77**:378–380. doi: 10.1136/jnnp.2005.070714

Background: The natural history and triggers of perihematoma oedema (PHO) remain poorly understood. Cerebral amyloid angiopathy (a common cause of lobar haemorrhage) has localised anticoagulant and thrombolytic properties, which may influence PHO. We hypothesised that early (within 24 hours) oedema to haematoma volume ratios are smaller in patients with lobar intracerebral haemorrhage (ICH) than in patients with deep ICH.

Methods: Haematoma and PHO volumes were measured in consecutive patients admitted to an acute stroke unit with a diagnosis of spontaneous supratentorial ICH proven by computed tomography. The oedema to haematoma volume ratios were calculated and compared in patients with lobar ICH and deep ICH.

Results: In total, 44 patients with ICH were studied: 19 patients had deep ICH, median haematoma volume 8.4 ml (interquartile range (IQR) 4.8 to 20.8), median PHO 8.2 ml (2.8 to 16), and 25 had lobar ICHs, median haematoma volume 17.6 ml (6.6 to 33.1) and median oedema volume 10.2 ml (3.4 to 24.2). Patients with lobar ICH were older than those with deep ICH (65.7 v 57.4 years, $p=0.009$) but ICH location did not differ by sex or race. There was no evidence that haematoma or oedema volumes were related to type of ICH ($p=0.23$, $p=0.39$ respectively). The median oedema to haematoma volume ratios were similar in patients with lobar and deep ICH (0.67 v 0.58 , $p=0.71$). Controlling for age, sex, and race made little difference to these comparisons.

Conclusions: There are no major location specific differences in PHO volumes within 24 hours of ICH onset. Deep and lobar ICH may have common therapeutic targets to reduce early PHO.

Intracerebral haemorrhage (ICH) usually results from rupture of small parenchymal arterioles. Neurological deficits are either maximum at time of stroke onset or evolve over the following minutes. Computerised tomography (CT) scans have demonstrated ongoing bleeding, which may continue in 38% of patients during the first 24 hours after ICH onset and result in further neurological deterioration.¹ Haematoma expansion after 24 hours is unusual. Although perihematoma oedema (PHO) has been associated with neurological deterioration,² there has been limited investigation of PHO to date compared with investigation of haematomas per se.^{3,4}

Most spontaneous ICH, particularly those due to hypertension, are located deep within the basal ganglia or thalamus. ICH within the cortical and corticostriatal (lobar) region may result from cerebral amyloid angiopathy (CAA). Such haemorrhages occur in older patients and have a higher recurrence rate compared to deep hypertensive ICH. In CAA, deposition of amyloid β protein replaces smooth muscle cells. Increasing amounts of cellular amyloid precursor protein

attach to amyloid β protein. Amyloid precursor protein inhibits factors IXa and VIIa of the clotting cascade, which may result in a local anticoagulant microenvironment.⁵ In addition, tissue plasminogen activator activity is increased by fibrillar amyloid β peptides. CAA may therefore upregulate local proteolytic (anticoagulant and thrombolytic) mechanisms.⁵

There is less PHO in patients with thrombolysis related ICH⁶ than in patients with ICH who have not been treated with a thrombolytic drug. Patients with ICH who are anticoagulated also appear to have less PHO than ICH patients who are not anticoagulated.⁷ Because anticoagulation and thrombolysis are associated with less PHO than other forms of ICH, we hypothesised that patients with lobar ICH (who usually have CAA) have smaller PHO volumes than patients with deep ICH. We therefore compared early PHO volume as a ratio of haematoma volume in different brain locations in patients admitted to hospital with a diagnosis of spontaneous ICH.

METHODS

The study was approved by the institutional review board of Duke University. Prior to enrolment, patients or a relative provided informed consent or assent, respectively.

Consecutive patients admitted to an acute stroke unit with a diagnosis of ICH proven by CT were studied. Baseline CT scan of brain was performed on admission, which occurred within 24 hours of ICH onset.

Details of the study have been previously described.² PHO and ICH volumes were measured using a modified version of the ABC/2 method.⁸ Briefly, the surface area of the hyperdensity observed on CT was calculated manually from a grid for each axial slice. This was multiplied by the thickness of the axial slice, and the volumes of all the slices were then added. PHO volumes (rim of hypodensity) were calculated by subtracting the ICH volume from the combined ICH and PHO volumes. All CT volumes were measured by one investigator (MOM).

Patients were included in the study if they had a supratentorial ICH documented by CT within 24 hours of onset and no intraventricular haemorrhage or surgical intervention. Patients with ICH due to trauma, any form of anticoagulation, central nervous system tumours, arteriovenous malformations, or thrombolytic therapy were excluded. The resulting study group comprised patients with ICH attributed to hypertension or possible/probable cerebral amyloid angiopathy.

Statistical analyses

Age, sex, race, location of haemorrhage, admission haematoma oedema volumes were determined. A neuroradiologist documented ICH location. Intraobserver reliabilities for haematoma and PHO volumes were determined from

Abbreviations: CAA, cerebral amyloid angiopathy; CT, computed tomography; ICH, intracerebral haemorrhage; MMP, matrix metalloproteinase; PHO, perihematoma oedema

repeated measurements of 18 CT scans by computing the intraclass correlation coefficient. Inspection of the distributions of ICH and PHO volumes and ICH:PHO volume ratios showed these to be positively skewed, and they were therefore log transformed prior to statistical analyses. Baseline characteristics of individuals with deep and lobar ICHs were compared using χ^2 (race (black, white) and sex) and *t* tests (age, natural logarithms of ICH and PHO volumes, and ICH:PHO volume ratios). Linear regression was used to compare log transformed ICH and PHO volumes and ICH:PHO volume ratios, adjusting for age, sex, and race. Analyses were performed using Stata (version 8.0; Stata Corp., College Station, TX, USA) and SPSS software (version 10.0; SPSS, Chicago, IL, USA).

RESULTS

In total, 101 patients with deep or lobar ICH were screened for inclusion. Excluded patients had thrombolysis related ICH (*n* = 8), intraventricular ICH (*n* = 43), posterior fossa ICH (*n* = 2), or a combination of posterior fossa and intraventricular ICH (*n* = 4). Thus, 44 patients fulfilled the criteria for assessment of oedema to haematoma volume ratios. Of these, 25 had lobar ICHs. One patient had a recurrence in a different location and was eligible for two enrolments in the study. Three patients presented with two simultaneous lobar ICHs, and 19 patients had deep ICHs confined to the basal ganglia and/or thalamus.

The intraclass correlation coefficients demonstrated excellent intraobserver reliability (0.998, 95% confidence interval (CI) 0.995 to 0.999 for haematomas and 0.959, 95% CI 0.897 to 0.984, for PHO.) The demographic details and CT findings are shown in table 1. Patients with lobar ICH were older than those with deep ICH. As ICH and PHO volumes were positively skewed, the median (interquartile range) values are shown. Although patients with lobar ICH had higher median ICH and PHO volumes than patients with deep ICH, neither of these differences nor the PHO:ICH volume ratios were statistically significant in unadjusted analyses. Furthermore controlling for age, sex, and race did not alter the comparisons between deep and lobar ICH for haematoma volume (*p* = 0.124), PHO volume (*p* = 0.409) or PHO:ICH volume ratio (*p* = 0.496). Repeat analyses without the second ICH from one patient also did not alter the results (ICH volume, *p* = 0.133; PHO volume, *p* = 0.407; and PHO:ICH volume ratio, *p* = 0.511).

DISCUSSION

This study has shown that there are no major location specific quantitative differences in the volume of early (within 24 hours) PHO relative to haematoma volume. This finding suggests that the net result of the initial triggers for

PHO in patients with spontaneous ICH are similar in both deep and cortical or lobar regions. There has been little research into the clinical effects of PHO; until recently it was thought to have only deleterious effects, but in at least one study, relative PHO measured within 24 hours has been shown to be an independent predictor of improved functional outcome.⁴

Several mechanisms have been described for different stages of PHO formation.⁷ Within the first few hours hydrostatic pressure and clot retraction may result in oedema. A second phase of PHO during the first 2 days results from activation of the coagulation cascade (an effect that may be enhanced by amyloid β protein⁵) and thrombin production.⁹ We had hypothesised that amyloid β protein in cortical blood vessels may discourage oedema formation by a local anticoagulant effect and promotion of tissue plasminogen activator activity. Hirudin, a specific thrombin inhibitor, inhibits PHO formation in a rat ICH model.⁹ Argatroban, another thrombin inhibitor, has also been proposed to reduce PHO formation,¹⁰ although thrombin may remain within the haematoma. Further understanding of early PHO development has recently been derived from MRI research, which demonstrated that early PHO volume is directly proportional to the rate of diffusion.¹¹ Increased oncotic pressure from excess proteins may drive this process.

Amyloid β protein is known to stimulate the expression of matrix metalloproteinase-9 (MMP-9), which has been implicated in many processes involved in disruption of the blood-brain barrier. Circulating levels of MMP-9 are raised following spontaneous ICH, peaking at around 48 hours, and predict early development of ICH.¹² A positive association has been demonstrated between circulating MMP-9 levels and PHO.¹³ However, many other proteolytic mechanisms have been identified in the complex process of PHO formation. For example, inhibition of complement activation with *N*-acetylheparin and systemic complement depletion¹⁴ have been shown to attenuate PHO in experimental models.

It has yet to be established whether the third phase of PHO formation, which occurs after 3 days due to red cell lysis, haemoglobin breakdown, and haemoglobin induced neuronal toxicity, has location specific quantitative characteristics.⁷ A peak in PHO volume between days 3 and 4¹⁵ may explain late deterioration from ICH. The evolution of PHO may therefore offer a time window during which therapies may be introduced to reduce late oedema formation and improve outcome.

There are some limitations to our study. Although not pathologically proven, the age profile of patients with lobar ICH (compared to patients with deep ICH) as well as the presence of multiple and recurrent ICHs in the lobar ICH group suggest that these patients had many of the characteristics of CAA related haemorrhage. The study selection criteria inevitably reduced the number of eligible patients from the ICH database. However, supratentorial ICH patients without surgery or intraventricular extension permitted a better defined examination of location specific PHO characteristics. Any mixing with cerebrospinal fluid risked confounding oedema measurements and the evolution of PHO formation. Although lobar haemorrhages were larger than deep haemorrhages, this may have been due to the selection of haemorrhages without intraventricular extension; the ICH in patients with larger deep ICHs may have been more likely to extend intraventricularly resulting in these patients being excluded from the study. Analyses of larger ICH datasets are required to confirm our findings and to determine whether later PHO volumes have location specific quantitative differences. Further understanding of the biological processes involved in the development of PHO,

Table 1 Demographic characteristics and CT scan findings in patients with supratentorial intracerebral haemorrhage (ICH)

	Deep ICH	Lobar ICH	p
Number	19	25	–
Mean (SD) age, years	57.4 (9.9)	65.7 (10.0)	0.009
Male sex, n (%)	12 (63.2)	12 (48.0)	0.32
Race: Black, n (%)	8 (42.0)	9 (38.0)	0.78
Median ICH volume, ml (IQR)	8.4 (4.8 to 20.8)	17.6 (6.6 to 33.1)	0.23
Median perihematoma oedema, ml (IQR)	8.2 (2.8 to 16.0)	10.2 (3.4 to 24.2)	0.39
Median PHO:ICH volume, ml (IQR)	0.58 (0.44 to 1.02)	0.67 (0.45 to 0.95)	0.71

IQR, interquartile range.

including development beyond 24 hours, may identify potential targets amenable to therapeutic intervention.

ACKNOWLEDGEMENTS

P McCarron is supported by a career scientist award funded by the Research and Development Office for Health and Personal Social Services in Northern Ireland.

Authors' affiliations

M O McCarron, Department of Neurology (MOM), Altnagelvin Hospital, Londonderry, UK

P McCarron, Department of Epidemiology and Public Health Medicine (PMC), Queen's University of Belfast, Belfast, UK

M J Alberts, Department of Neurology (MJA), Room 1420, Northwestern University Medical School, 710 North Lake Shore Drive, Chicago, IL, USA

Competing interests: none

Correspondence to: Dr Mark McCarron, Department of Neurology, Altnagelvin Hospital, Londonderry, BT47 6SB, UK; markmccarron@doctors.org.uk

Received 27 April 2005

In revised form 4 August 2005

Accepted 5 August 2005

REFERENCES

- 1 **Brott T**, Broderick J, Kothari R, *et al*. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 1997;**28**:1–5.
- 2 **McCarron MO**, Hoffmann KL, DeLong DM, *et al*. Intracerebral hemorrhage outcome: apolipoprotein E genotype, hematoma, and edema volumes. *Neurology* 1999;**53**:2176–9.
- 3 **Gebel JMJ**, Jauch EC, Brott TG, *et al*. Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke* 2002;**33**:2631–3.
- 4 **Gebel JMJ**, Jauch EC, Brott TG, *et al*. Relative edema volume is a predictor of outcome in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke* 2002;**33**:2636–41.
- 5 **McCarron MO**, Nicoll JAR. Cerebral amyloid angiopathy and thrombolysis-related intracerebral haemorrhage. *Lancet Neurol* 2004;**3**:484–92.
- 6 **Gebel JM**, Brott TG, Sila CA, *et al*. Decreased perihematomal edema in thrombolysis-related intracerebral hemorrhage compared with spontaneous intracerebral hemorrhage. *Stroke* 2000;**31**:596–600.
- 7 **Xi G**, Keep RF, Hoff JT. Pathophysiology of brain edema formation. *Neurosurg Clin N Am* 2002;**13**:371–83.
- 8 **Kothari RU**, Brott T, Broderick JP, *et al*. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996;**27**:1304–5.
- 9 **Lee KR**, Colon GP, Betz AL, *et al*. Edema from intracerebral hemorrhage: the role of thrombin. *J Neurosurg* 1996;**84**:91–6.
- 10 **Hamada R**, Matsuoka H. Antithrombin therapy for intracerebral hemorrhage. *Stroke* 2000;**31**:794–5.
- 11 **Butcher KS**, Baird T, MacGregor L, *et al*. Perihematomal edema in primary intracerebral hemorrhage is plasma derived. *Stroke* 2004;**35**:1879–85.
- 12 **Silva Y**, Leira R, Tejada J, *et al*. Molecular signatures of vascular injury are associated with early growth of intracerebral hemorrhage. *Stroke* 2005;**36**:86–91.
- 13 **Abilleira S**, Montaner J, Molina CA, *et al*. Matrix metalloproteinase-9 concentration after spontaneous intracerebral hemorrhage. *J Neurosurg* 2003;**99**:65–70.
- 14 **Xi G**, Hua Y, Keep RF, *et al*. Systemic complement depletion diminishes perihematomal brain edema in rats. *Stroke* 2001;**32**:162–7.
- 15 **Enzmann DR**, Britt RH, Lyons BE, *et al*. Natural history of experimental intracerebral hemorrhage: sonography, computed tomography and neuropathology. *Am J Neuroradiol* 1981;**2**:517–26.