Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia

C L Shovlin,1,4 J E Jackson,5 K B Bamford,2,6 I H Jenkins,7 A R Benjamin,4 H Ramadan,4 E Kulinskaya3

ABSTRACT

Background: Brain abscesses and ischaemic strokes complicate pulmonary arteriovenous malformations (PAVMs). At risk individuals are poorly recognised. Stroke/abscess risk factors have not been defined.

Methods: A cohort study of 323 consecutive individuals with PAVMs (n = 219) and/or the commonly associated condition hereditary haemorrhagic telangiectasia (HHT, n = 305) was performed. Most of the 201 individuals with PAVMs and HHT had no respiratory symptoms, and were unaware they had HHT. Anderson–Gill models assessed constant and time dependent potential predictive variables for stroke/abscess, and rate reduction by PAVM embolisation.

Results: 57 individuals with PAVMs and HHT experienced brain abscess or ischaemic stroke, usually prior to the diagnosis of underlying PAVMs/HHT. The primary determinants of stroke and abscess risks were unrelated to severity of PAVMs. Males had higher brain abscess rates (hazard ratio 3.61 (95% CI 1.58, 8.25), p = 0.0024; intervention histories and bacteriological isolates suggested dental sources. Once adjusted for gender, there was a marginal association between brain abscess and low oxygen saturation. For ischaemic stroke, there was no association with any marker of PAVM severity, or conventional neurovascular risk factors. Surprisingly, low mean pulmonary artery pressure was strongly associated with ischaemic stroke (hazard ratio 0.89 (95% CI 0.83, 0.95) per mm Hg increase; p = 6.2 × 10−5). PAVM embolisation significantly reduced ischaemic stroke rate (p = 0.028); no strokes/abscesses occurred following obliteration of all angiographically visible PAVMs. The mean PAVM diagnosis–treatment interval was longer, however, when neurological risks were unrecognised.

Conclusions: Ischaemic strokes and brain abscesses occur commonly in undiagnosed HHT patients with PAVMs. Risk reduction could be improved.

Pulmonary arteriovenous malformations (PAVMs) are abnormal dilated vessels which provide a right-to-left (R-L) shunt between the pulmonary arterial and venous circulations.1 Ischaemic strokes and brain abscesses affect high proportions of patients with PAVMs.2 4 Embolisation can be used to treat PAVMs if the condition is recognised;2 4 6 but until now, no direct evidence for reduction of brain abscess or stroke incidence has been presented. Antibiotic prophylaxis prior to dental and surgical interventions has been suggested.5 Many patients with a diagnosis of PAVMs are offered no treatment or prophylaxis as the risks of stroke and brain abscess are poorly appreciated, and were not mentioned in a recent authoritative set of guidelines for stroke prevention.9 PAVMs affect greater numbers of individuals than expected, particularly in association with hereditary haemorrhagic telangiectasia (HHT, also known as Osler–Weber–Rendu syndrome). This relatively common inherited condition has a prevalence of 1 in 5000–8000.10 11 HHT leads to nose bleeds, characteristic mucocutaneous telangiectasia, gastrointestinal bleeding and multiple AVMs in pulmonary, cerebral and hepatic circulations.12 13 PAVMs are usually present by adult life.7 With improved screening methods (CT scans and angiography verification), the cited frequency of PAVMs in HHT has risen from 5–15%12 13 to at least 48%,1 suggesting there may be 3000–5000 individuals with PAVMs in a country of 60 million inhabitants.

Understanding which individuals with PAVMs are at risk of neurological complications is important in order to facilitate appropriate PAVM management strategies. In addition, as ischaemic stroke and brain abscess are attributed to paradoxical embolic events through PAVM R-L shunts,12 PAVMs offer the opportunity to explore mechanisms potentially relevant to other more common conditions, such as patent foramen ovale.9 16 This condition affects up to 27% of adults16; why only a small proportion of the population with patent foramen ovale suffer paradoxical embolic strokes is unknown.

Study of individuals with PAVMs however, carries all the difficulties encountered in studies of rare disease.17 In particular, the relatively small number of affected patients (fewer than 500 reported in the world literature prior to 199018, 27 referred to BTS BOLD project between 1999–2007) limits the statistical power of many studies, particularly if the complication under study is predicted to occur in less than 25% of patients over decades, as for strokes and brain abscess in patients with PAVMs.10

Here we report an approach in this rare condition that allowed three major questions to be addressed: firstly, whether risk factors could be established to predict which individuals were at higher stroke/abscess risk; secondly, whether stroke/abscess could be prevented by conventional PAVM embolisation techniques; and thirdly,
whether increased physician awareness of PAVM risks would be needed to optimise risk reduction strategies.

METHODS
Study design and patient population
In view of the known risks for the PAVM population, in 1999, prior to return to Hammersmith Hospital, London, UK, CLS designed a study on stroke outcomes for patients to be reviewed from 1 May 1999. Randomisation of patients to treatment and no treatment arms was considered unethical in view of the known benefits of embolisation in reducing PAVM size, R-L shunt and hypoxaemia. \(^\text{2,3,6,7,10}\) Inclusion of strokes/abscesses occurring only after review was recognised as impractical because of the expected rates of patient referral and complications. All clinical strokes occurring prior to review and treatment, or subsequently, were therefore recorded. The study recruitment period ended in May 2005 when 442 patients had been reviewed in the service. Follow-up continued until 31 May 2006.

Stroke analyses
Aetiologies were assigned for all clinical strokes (focal cerebral deficit of rapid onset of >24 h in duration with no apparent cause other than a vascular one) occurring prior to review and treatment, or in the follow-up period: a diagnosis of brain abscess was made locally at the time of the event. All cases required neurosurgical drainage and prolonged intravenous antibiotics. Ischaemic strokes were defined by neurologists either locally (n = 26) or by retrospective review of imaging reports and medical notes (n = 5). Sixteen further strokes were excluded from subsequent analyses as cerebral haemorrhage attributed to cerebral AVMs was either definite (n = 7) or could not be excluded (n = 9). Some definitions required supplementary information which was obtained from other institutions with patient consent.

Individuals who had experienced a brain abscess were asked to complete an ethically approved patient questionnaire regarding details of their dental and general health in the year leading up to their abscess. Patients were offered choices of “all, some, none or not sure” for the number of (i) their own teeth, (ii) fillings and (iii) crowns or caps; and “good, poor or not sure” for (iv) teeth and gum state. They were also asked to tick whether they had undergone (or were not sure of) any (v) fillings, (vi) extractions, (vii) scale and polish procedures, (viii) other dental interventions or (ix) surgical procedures and, if so, how long before the abscess. Supplementary information regarding microbiology and neurological details was obtained from other institutions with patient consent. Positive microbiology results from three further PAVM/brain abscess patients reviewed during the follow-up year were included.

Neurovascular risk factors
Current or ex-smoking status, hypertension on treatment or blood pressure >140/90, atrial fibrillation on treatment or ECG, and known diabetes mellitus, hypercholesterolaemia or cardiac disease were recorded. Headaches were defined as migrainous for patients on migraine treatment or describing recurrent headaches with aura and/or tachycardia. Noting the paradoxical embolic aetiology of PAVM associated ischaemic strokes and brain abscess, the occurrence of deep venous thrombosis or pulmonary embolus (DVT/PE), haemoglobin (Hb) and baseline disease were recorded. Headaches were defined as migrainous for patients on migraine treatment or describing recurrent headaches with aura and/or tachycardia. Noting the paradoxical embolic aetiology of PAVM associated ischaemic strokes and brain abscess, the occurrence of deep venous thrombosis or pulmonary embolus (DVT/PE), haemoglobin (Hb) and baseline disease were recorded.

Statistical analyses
A coded database was established for entry of primary data from hospital records and computer reports. For calculations of age dependent incidence rates, the total number of years provided by each patient per decade of life was calculated, and the number of events in that decade expressed as a rate per thousand patient years. For relative risk analyses, age dependent incidence rates were recalculated for age groupings, as presented in general population series from a comparable UK population and a general US population. A crude estimate of relative risk was obtained by comparison of the PAVM and general population incidence rates for each age group.

All other analyses were performed analysing the 219 PAVM patients separately, and included all periods from birth
onwards. Second abscess/ischaemic strokes and peri-embolisation stroke were excluded from all incidence, risk factor and referral pattern analyses. To exclude ascertainment bias, patients whose PAVMs were diagnosed as a result of their abscess or stroke were excluded from incidence rate and pre/post treatment analyses. Survival curves included second strokes, but excluded patients whose PAVMs were diagnosed as a result of their abscess or stroke. Treatment delay analyses excluded PAVMs diagnosed before 1985, when surgery might have been considered the only therapeutic option. Basic statistics and univariate analyses were performed using Prism 4 (Graph Pad Software Inc, San Diego, California, USA).

Continuous variables were compared by the two sided Mann–Whitney test and binary variables using Fisher’s exact test. For analysis of four way presentation patterns, overall p values were calculated by ANOVA with Bonferroni post-test corrections applied.

To define stroke/abscess associations and efficacy of embolisation in a population with time varying variables, including point of embolisation, an extension of Cox proportional hazards regression model, Anderson–Gill, suitable for the analysis of recurrent events was fitted with embolisation as a time dependent covariate using SPLUS 6. The Anderson–Gill model can be fitted to non-constant, but proportional hazards. The intra-subject correlation inherent in a study of multiple events for the same subject is accounted for by a robust grouped jackknife variance estimator. The Anderson–Gill model has been recommended for two main reasons: its efficiency and the reliability of the overall treatment effect.

Several contiguous time intervals between events (ischaemic stroke, abscess, embolisation and/or last follow-up) were defined per patient with age at the end of interval defined. Values of 25 potential predictory variables (constant or time dependent) were assigned to each interval, in four groups: certain values were assigned variably but definitely to intervals according to the documented age of onset (for HHT, use of iron, transfusions, female hormones or tranexamic acid; neurovascular risk factors, migraine, current or ex-smoker, hypertension, diabetes mellitus, atrial fibrillation, hypercholesterolaemia and cardiac disease; and PAVM features at the time of stroke/abscess for patients experiencing these after assessment/treatment for PAVMs). Otherwise, PAVM severity markers (symptoms, SaO2, R-L shunt, PAVM multiplicity, diameter of largest feeding artery, presence of small untreatable PAVMs) were assumed to be constant up to the point of first presentation/
treatment, since post development (usually at puberty), PAVMs remain relatively stable.\(^2,3\) Other variables were assumed to be constant across all intervals (gender, susceptibility to DVT/PE as long term risk predictions are established for the population\(^7\); symptomatic cerebral or hepatic AVMs, as CAVMs develop perinatally and there are no data regarding age of onset for HAVMs).\(^3\) For three variables, Hb, factor VIII:Ag\(^2\) and mean PAP, first recorded measurements were initially assigned across all intervals, although it was recognised that there are age dependent components to these variables. Pilot analyses indicated significant associations of mean PAP and Hb with ischaemic stroke. For final analyses and models therefore, mean PAP and Hb were defined for each interval as the median of interval measurements \(>3\) months apart, or appropriately age adjusted/extrapolated: PAP increases with age (mean PAP = \(0.071 + 0.131 \times \text{[age]}\) in this population, manuscript in review): for \(33\) PAP data points, adjustments of \(1-4\) mm Hg were made for age. Hb was recorded \(0-30\) times per patient, falling in \(32\) cases.

### RESULTS

**Patient population**

Between 1 May 1999 and 30 May 2005, definite diagnoses of PAVMs and HHT\(^7\) were established in 219 and \(305\) cases, respectively; 93.6% (208/219) of PAVM patients had HHT (details available). A diagnosis of HHT was not made for \(6.4\%\) (14/219) of individuals with PAVMs with no personal or family features of HHT other than occasional nose bleeds. The 219 PAVM patients were referred by 122 doctors from 18 specialties, and more than 117 primary care trusts. Sixty were referred by general practitioners, 159 were referred for PAVM management and 80 were diagnosed by inhouse PAVM screening investigations.

Most patients with PAVM had no significant respiratory symptoms: 79.5% (173/219; CI 73.1, 84.0%) were diagnosed by incidental investigations (35.3%; 73/219; CI 27.0, 40.0%) or PAVM screening programmes in families with HHT (45.7%; 100/219; CI 38.6, 51.9%). Only 21.5% (46/219; CI 16.0, 26.9%) of individuals had PAVMs diagnosed by chest x ray, CT scan or oxygenation measurements performed because of respiratory symptoms. Most PAVM patients with HHT (59%; 121/205; CI 52.2, 65.5%) were unaware that they had HHT at the time of PAVM diagnosis.

Seventy-four (33.8%) individuals with PAVMs had a brain abscess or clinical stroke, either prior to review and treatment or in the follow-up period. Twenty-eight patients had at least one brain abscess, and 30 had at least one proven ischaemic stroke. Six patients had more than one event. All 57 abscess/isaemic stroke patients had underlying HHT (\(p = 0.023\), Fisher’s exact test), and there was only one event (ischaemic stroke) in a HHT patient without PAVMs. Strokes and abscesses commonly occurred in individuals before the diagnosis of HHT or PAVMs was made, and usually did not precipitate a diagnosis of PAVMs (table 1). Age dependent incidence rates and relative risk analyses of age dependent incidence rates compared with incidence rates reported in series from the general population are presented in fig 1.

### Brain abscess associations in PAVM patients

Brain abscess commonly occurred in asymptomatic individuals without a prior diagnosis of PAVM or HHT (table 1). In this series, while all survived, 80% (12/15) were unable to return to their former occupation because of persistent neurological deficits (table 1). Univariate analyses identified no significant relationship between brain abscess and any of the six markers of PAVM severity (table 2). To illustrate this unexpected finding further, the number of individuals experiencing a brain abscess was examined as a categorical variable for two commonly used clinical parameters of PAVM severity, oxygenation reflecting the size of the R-L shunt and the diameter of the largest feeding artery to PAVMs (see supplementary fig S1Aii, ii online). Although no association with PAVM severity markers was identified, univariate analyses suggested significant associations with male sex (\(p = 0.0054\)) and DVT (\(p = 0.0186\)) (see

---

**Table 2** Univariate associations of PAVM variables with brain abscess and ischaemic stroke

<table>
<thead>
<tr>
<th>Brain abscess</th>
<th>N with/without abscess</th>
<th>Event</th>
<th>Event free group</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS presentation (%) (n (%))</td>
<td>28/190</td>
<td>5 (17.9)</td>
<td>42 (22.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>(\text{SaO}_2) (%) (median [Q1, Q3])</td>
<td>21/163</td>
<td>93.0 (86.5, 96)</td>
<td>93.8 (89.0, 96.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>R-L (%) (median [Q1, Q3])</td>
<td>20/111</td>
<td>9.3 (3.1, 22)</td>
<td>9.2 (5.0, 19.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Single PAVMs* (%) (n (%))</td>
<td>27/195</td>
<td>7 (25.9)</td>
<td>45 (24.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Largest fad (mm) (median [Q1, Q3])</td>
<td>24/164</td>
<td>5.5 (3.0, 8.5)</td>
<td>5 (4.0, 8.5)</td>
<td>0.37</td>
</tr>
<tr>
<td>Small (fad &lt; 3 mm) (%) (n (%))</td>
<td>28/190</td>
<td>21 (75.0)</td>
<td>140 (73.7)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ischaemic stroke</th>
<th>N with/without stroke</th>
<th>Event</th>
<th>Event free group</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS presentation (%) (n (%))</td>
<td>30/186</td>
<td>8 (26.7)</td>
<td>39 (21)</td>
<td>0.48</td>
</tr>
<tr>
<td>(\text{SaO}_2) (%) (median [Q1, Q3])</td>
<td>25/157</td>
<td>93 (85, 96)</td>
<td>94 (88.5, 96)</td>
<td>0.3</td>
</tr>
<tr>
<td>R-L (%) (median [Q1, Q3])</td>
<td>24/105</td>
<td>11.0 (7.1, 19.5)</td>
<td>8.8 (4.7, 20.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Single PAVMs* (%) (n (%))</td>
<td>29/181</td>
<td>7 (24.1)</td>
<td>44 (24.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Largest fad (mm) (median [Q1, Q3])</td>
<td>28/158</td>
<td>5.5 (4.0, 7.5)</td>
<td>5 (3.0, 6.0)</td>
<td>0.087</td>
</tr>
<tr>
<td>Small (fad &lt; 3 mm) (%) (n (%))</td>
<td>29/187</td>
<td>24 (82.8)</td>
<td>137 (73.3)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*More common in non-HHT patients (\(p < 0.0001\), Fisher’s exact test two sided \(p\) value). fad, feeding artery diameter; HHT, hereditary haemorrhagic telangiectasia; PAVM, pulmonary arteriovenous malformations; R-L, right-to-left; RS, respiratory symptoms; \(\text{SaO}_2\), arterial oxygen saturation.

---

* Thorax 2008;63:259–266. doi:10.1136/thx.2007.087452

---

supplementary table S1 online) which always occurred in the months following abscess neurosurgical drainage.25

Recognising the strong relationship between age and brain abscess risk (fig 1), Cox proportional hazard models (Anderson–Gill) were fitted with embolisation as a time dependent covariate (table 3). The best models confirmed male sex as a significant risk factor for brain abscess. The hazard ratio for untreated men was 3.61 (95% CI 1.58, 8.25; p = 0.047), and for all men, including pre and post embolisation patient periods, 3.49 (95% CI 1.43, 8.33; p = 0.017) (table 3, see also supplementary fig S2 online). DVT was also significantly associated, since brain abscess and/or sequelae appear to precipitate DVT in DVT susceptible patients (see supplementary table S2 online). As in other series,34 the majority of abscess cultures were sterile. The principal isolates were microaerophilic and anaerobic bacteria, including *Porphyromonas* spp, *Propionibacterium* spp, *Actinomyces meyeri*, *Peptostreptococcus* spp, *Bacteroides* spp and members of the *Sireptococcus milleri* group that are commonly isolated in endo and periodontal infections (see supplementary table S2 online). Polymicrobial infections were present in 50% of culture positive aspirates. Only one of the patients had a concurrent contiguous infection (otitis media). In contrast with the high risk cardiac patients with infective endocarditis,35 a high proportion of the PAVM brain abscess group had experienced identifiable events that are known to be associated with bacteraemia in the weeks preceding their abscess, particularly occlusive braces and fillings (n = 4) (see supplementary table S3 online).

**Ischaemic stroke associations**

Ischaemic stroke also commonly occurred in asymptomatic individuals without a prior diagnosis of PAVM or HHT (table 1). Univariate analyses identified no significant relationship between any PAVM parameter and the incidence of ischaemic stroke (table 2 and supplementary fig S1Bi, ii online). Classical neurovascular risk factors did not emerge as risk factors, nor did any association with size of feeding artery (see supplementary table S2 model 3 online) or other PAVM variables (data not shown).

As in other series,34 the majority of abscess cultures were sterile. The principal isolates were microaerophilic and anaerobic bacteria, including *Porphyromonas* spp, *Propionibacterium* spp, *Actinomyces meyeri*, *Peptostreptococcus* spp, *Bacteroides* spp and members of the *Sireptococcus milleri* group that are commonly isolated in endo and periodontal infections (see supplementary table S2 online). Polymicrobial infections were present in 50% of culture positive aspirates. Only one of the patients had a concurrent contiguous infection (otitis media). In contrast with the high risk cardiac patients with infective endocarditis,35 a high proportion of the PAVM brain abscess group had experienced identifiable events that are known to be associated with bacteraemia in the weeks preceding their abscess, particularly occlusive braces and fillings (n = 4) (see supplementary table S3 online).

### Table 3 Anderson–Gill models for brain abscess and ischaemic stroke

<table>
<thead>
<tr>
<th>Model</th>
<th>n</th>
<th>df</th>
<th>R²</th>
<th>p value for test</th>
<th>Wald test p value</th>
<th>Robust score p value</th>
<th>Hazard ratio for variable (95% CI)</th>
<th>p value for variable in model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain abscess</td>
<td>217</td>
<td>2</td>
<td>0.047</td>
<td>1.2 × 10⁻³</td>
<td>1.76 × 10⁻²</td>
<td></td>
<td>3.61 (1.58, 8.25)</td>
<td>2.4 × 10⁻²</td>
</tr>
<tr>
<td>Gender (male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.35 (1.32, 8.50)</td>
<td>0.011</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>178</td>
<td>1</td>
<td>0.036</td>
<td>6.1 × 10⁻⁴</td>
<td>3.20 × 10⁻³</td>
<td></td>
<td>0.89 (0.83, 0.95)</td>
<td>6.2 × 10⁻⁴</td>
</tr>
<tr>
<td>PAP mean (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain abscess</td>
<td>392</td>
<td>1</td>
<td>0.017</td>
<td>6.3 × 10⁻³</td>
<td>9.50 × 10⁻³</td>
<td></td>
<td>3.49 (1.43, 8.33)</td>
<td>6.3 × 10⁻²</td>
</tr>
<tr>
<td>Gender (male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>250</td>
<td>4</td>
<td>0.051</td>
<td>4.7 × 10⁻²</td>
<td>2.00 × 10⁻²</td>
<td></td>
<td>0.85 (0.79, 0.92)</td>
<td>6.0 × 10⁻⁵</td>
</tr>
<tr>
<td>PAP mean (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embolisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95 (0.72, 1.27)</td>
<td>0.75</td>
</tr>
<tr>
<td>Embolisation × Hb (g/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.7 × 10⁻⁴ (7.55 × 10⁻⁴, 0.4)</td>
<td>0.028</td>
</tr>
<tr>
<td>Embolisation × embolisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.84 (1.1, 3.07)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

*Includes pre and post embolisation periods.

df degrees of freedom; Hb, haemoglobin; n, number of data points; PAP, pulmonary artery pressure.

**Figure 2** Anderson–Gill proportional hazards models for ischaemic stroke. Proportion surviving until first ischaemic stroke: p value for embolisation 0.028 (see table 3). (Brain abscess models are presented in supplementary fig S2 online.)
The high proportions of patients undiagnosed at the time of stroke/abscess highlight the importance of PAVM screening programmes for the HHT population. Chest x rays and oxygen measurements will not detect all clinically significant PAVMs. While discussion continues regarding the optimal mode of screening of individuals with HHT, expensive multiscale screening strategies have been proposed, the new generations of CT scanners mean that a diagnosis can be made efficiently and quickly using a thoracic CT scan. While the absolute number of events increased with increasing age (in view of the small numbers, we would not wish to over interpret the changes between individual groups), relative risks were higher for younger patients, highlighting the importance of screening in young adult life. Our data do not support PAVM screening for asymptomatic children: the only child or teenager with any neurological complication had extensive

**DISCUSSION**

The main and surprising finding of this series was that stroke/abscess risks could not be predicted by respiratory symptoms or PAVM severity in individuals with HHT and PAVMs. The data provide evidence for risk reduction by PAVM embolisation, indicate further potential preventative strategies for brain abscess but also highlight significant delays in diagnosis and referral for treatment of PAVMs.

The overall rates of brain abscess and ischaemic stroke are comparable with series reporting more than 30 PAVM cases. Brain abscess survival (100%) was remarkable, and reflected both a bias and an intervention: for patients experiencing prior abscesses, there was a bias due to survival to the time of PAVM clinic review. Following review by us, clinical risk of brain abscess was highlighted, as early diagnosis and intervention lead to better outcomes. We are unaware of any study stratifying stroke/abscess risk by PAVM or HHT symptoms, severity of hypoxaemia or R-L shunt. Univariate analyses of largest PAVM feeding artery diameter has been performed in a relatively small number of PAVM stroke patients.

Study strengths include the large number of individuals reviewed at a single institution, the use of consistent assessment methodologies (methods for R-L shunt measurements cannot be interchanged) and for the first time in any PAVM study, the use of proportional hazards models to analyse PAVM variables corrected for age and other parameters.

For a study indicating a major risk from small PAVMs, and lack of contribution from conventional neurovascular risk factors, there were several potential limitations. Firstly, some HHT/PAVM variables were extrapolated to earlier time points when the stroke/abscess occurred. This would, however, overestimate the severity of PAVMs as long term follow-up data of patients with residual PAVMs at our institution and elsewhere indicate that once present, PAVMs tend to remain relatively stable or increase in size, with only rare cases of spontaneous regression described. A second potential weakness was that formal screening for hypercholesterolaemia, cardiac disease and diabetes mellitus was not performed for the general PAVM population. Since such screening was performed at the time of stroke/abscess for all individuals with neurological complications, any bias would overestimate the contribution of these risk factors. We acknowledge that the lack of any observed influence of migraine, cerebral AVM or hepatic AVM may reflect the strict criteria used to define headaches as migrainous (although migraines were assigned to 41.4% of the population, and were more prevalent in individuals without ischaemic stroke), and lack of asymptomatic screening for cerebral and hepatic AVMs.

We therefore believe the study findings to be robust and important in defining management strategies for the PAVM population.
PAVMs which were diagnosed as a result of dyspnoea and cyanosis at the age of 2 years.

Once adjusted for age, there was no association between ischaemic stroke and PAVM feeding artery size, or any parameter measuring PAVM severity. For brain abscess, once adjusted for age and gender, there was only a marginal negative association with oxygen saturation, and no association with PAVM feeding artery size. These findings imply that asymptomatic individuals with small PAVMs have similar ischaemic stroke risks to the most cyanotic patients, although their risk of brain abscess may be marginally lower. The findings also imply that once the PAVM conduits are present, specific features and/or severity of PAVMs have minimal influence on the risk of neurological complications.

In our series, PAVM embolisation was a safe and effective procedure which prevented brain abscess and ischaemic stroke if complete occlusion of all PAVMs was achieved. Although only a marginal association was apparent between low oxygen saturation and brain abscess risk, this may support the use of embolisation to improve oxygenation, even if complete obliteration of all PAVMs cannot be achieved. There are technical limits to the size of the feeding artery that can be embolised by conventional coaxial transcatheter embolisation methods, and many individuals will have PAVMs that are too small to embolise. In our series which was not limited by the 3 mm “rule” recently questioned by others, 78% of patients had residual untreatable PAVMs, in keeping with other series. 6,7 These findings highlight the need for further stroke/abscess risk reduction strategies in PAVM patients.

For brain abscess, several lines of evidence point towards a pathogenic role for bacteriaemias of dental origin. Firstly, the majority of organisms identified are commonly and often specifically isolated in periodontal infections. 32 Secondly, there were potential precipitating events in many patients. 43 We recognise that it is difficult to determine whether a particular bacteriaemia associated event is the cause of a subsequent abscess, particularly for an indolent pathological process that may take months to present, and when the intensity of bacteriaemias during brushing and flossing may exceed those reducing the incidence of endocarditis in experimental models. 48

In keeping with a model of paradoxical embolic stroke, risk of HHT leads to increased genic steps that are thought to be targeted by antibiotic susceptibility to initial bacteriaemias or the subsequent pathogenic role for bacteriaemias. Firstly, the incidence of endocarditis was lower than in PAVM patients. Secondly, there were potential precipitating events in many patients. 43 We recognise that it is difficult to determine whether a particular bacteriaemia associated event is the cause of a subsequent abscess, particularly for an indolent pathological process that may take months to present, and when the intensity of bacteriaemias during brushing and flossing may exceed those reducing the incidence of endocarditis in experimental models. 48

In summary, PAVM size, severity and symptoms did not predict the risk of brain abscesses or ischaemic stroke, complications that occurred commonly in HHT patients with PAVMs. The study suggests that greater emphasis on HHT diagnosis, PAVM screening and PAVM treatment programmes are needed. For any PAVM patient presenting with a cerebrovascular event, the diagnosis of abscess should be considered even if the white cell count is normal (as in 60% of cases 14,33), since early diagnosis and intervention will lead to a better outcome. 44,44 The study also supports the use of antibiotic prophylaxis for interventional procedures, 3 and strategies to improve dental hygiene 50,50 as post extraction bacteriaemia is detected less frequently in healthy gums, 52 and there is a risk of “everyday” bacteriaemia. 52 PAVMs are usually silent, often difficult to diagnose and affect approximately 50% of individuals with HHT. It may therefore be appropriate to offer this advice to all individuals with HHT. As other R-L shunts such as patent foramen ovale are common in the general population, further exploration of factors that contribute to the risks of paradoxical embolic stroke and brain abscess in HHT/PAVM populations is warranted.

Acknowledgements: CLS and JEJ thank Georgina Rudd and Pam Brayshow for clinical secretarial services, Carin Mordin and other colleagues for lung function and imaging, and DJ Allison, JMB Hughes, TRG Rogers and AJ Newman Taylor for helpful discussions.

Ethics approval: None.

Competing interests: None.

Ethics approval: All studies were ethically approved by the Hammersmith, Queen Charlotte’s, Chelsea and Acton Hospital Research Ethics Committee (UIC 2000/5764).

REFERENCES


Pulmonary vasculature
Pulmonary vasculature


