Cerebral cavernous angioma: a potentially benign condition? Successful treatment in 16 cases

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Abstract
Cerebral cavernous angioma (cavernoma) has previously been treated by resection for all presentations when surgically resectable. In this retrospective series of 16 cases, it is demonstrated that, for those patients presenting with epilepsy alone, surgery is often unnecessary. Diagnosis can be made radiologically and excellent seizure control can be obtained with medications. In the authors' experience, those cavernomas symptomatic as epilepsy rarely cause major haemorrhage and the need for surgery as prophylaxis against bleeding in this group is unproven.

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Cavernomas of the central nervous system typically present as intracranial haemorrhage, epilepsy or as a mass lesion. Macroscopically these lesions have been likened to a ripe mulberry and microscopically are seen to consist of blood-filled cavities lined by a single layer of endothelium and separated by neuroglia, but not by neural tissue. Old haemorrhage and calcification are common. There are no other local vascular abnormalities.

Surgical excision has commonly been reported as appropriate treatment of cavernoma even though its clinical course remains poorly understood. Clinical series of those patients presenting with complications may overestimate the pathogenicity of the condition. The advent of MRI allows the reliable detection, follow up and diagnosis of asymptomatic and symptomatic cavernomas, thereby permitting a better understanding of the condition's natural course and appropriate management.

In this retrospective review of 16 patients in whom cavernous angiomas were diagnosed radiologically, we found that this lesion is often benign and produces little disability. In our opinion, resection is not necessarily the best treatment of cavernomas presenting as epilepsy.

Methods
Sixteen consecutive cases of cavernous angioma diagnosed by MRI at our hospital were reviewed retrospectively. The clinical features, investigations and treatment of each patient were gleaned from the hospital case notes or the records of the consulting physician. All patients with an MRI diagnosis of cavernoma were reviewed. All MRI scans were taken with a 1.5 Tesla Philips Gyroscan from which T1 and dual T2 weighted axial and coronal images were obtained. This particular machine was the only MRI scanner in the state and so this series represents all MRI-proven cavernomas in Western Australia over the review period.

Cavernous angiomata were diagnosed when MRI demonstrated a discrete lesion or lesions displaying central areas of differing signal intensity on T1 and T2 weighted images, indicative of haematomas of varying ages, focal fibrosis, focal calcification and a rim of low intensity at the periphery of the lesion. Haemosiderin was detected as areas of low signal intensity in T2 weighted images, thereby allowing discrimination from a flow void. The presence of a feeding artery or draining vein or neural tissue within the malformation was taken to exclude the diagnosis of cavernoma.

This series is based upon the use of an MRI scanner which services the entire state and is used by all neurologists and neurosurgeons, and consequently accurately represents all or most cavernomas presenting as epilepsy during the time of review. The absence of supratentorial cavernomas presenting with cerebral haemorrhage in this series presumably reflects our entry criterion requiring diagnosis by MRI and, as such, will underestimate their incidence. Such cavernomas may be lethal, or resected after an initial CT scan only. They were not included in this series because of lack of systematic access to necropsy and pathology data and their incidence in our community remains unknown. As all cases with an MRI diagnosis of cavernoma were reviewed, we are confident that no patient initially presenting with epilepsy sustained a subsequent, symptomatic cerebral haemorrhage.

Results
Presenting complaint and initial investigations
Sixteen cases consisting of eight males and eight females, with an average age at onset of 25.5 years and an average duration of seizures before diagnosis of 5.5 years (in the 15 symptomatic patients) were studied. Eight patients had had seizures for three or more years. Average follow up after diagnosis was three years (more than five years in four). Diagnosis was made by MRI in all and confirmed histologically in the two patients...
Figure 1  Cavernoma and adjacent cerebrum (patient 5; haematoxylin and eosin; magnification 4×2) showing fibrous capsule (small arrows), calcified haematoma (large arrow) and thin-walled vascular channels without intervening neuronal tissue.

Table 1  Clinical details of each patient with epilepsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Presenting complaint</th>
<th>Age at onset (years)</th>
<th>Time to diagnosis (years)</th>
<th>Follow up (years)</th>
<th>Treatment</th>
<th>Seizure control</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>CPS</td>
<td>14</td>
<td>3</td>
<td>11</td>
<td>PHY/CBZ</td>
<td>Rare</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>CPS</td>
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<td>10</td>
<td>4</td>
<td>CBZ</td>
<td>Rare</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>GTC*</td>
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<td>3</td>
<td>8</td>
<td>CBZ None</td>
<td>Rare</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>GTC</td>
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<td>0</td>
<td>5</td>
<td>CBZ</td>
<td>Rare</td>
</tr>
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<td>19</td>
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</tr>
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<td>7</td>
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<td>14</td>
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<td>1</td>
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<td>10</td>
<td>F</td>
<td>CPS</td>
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<td>5</td>
<td>1</td>
<td>PHY</td>
<td>Rare</td>
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<td>M</td>
<td>CPS/GTC</td>
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<td>1</td>
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<td>VAL/PHE</td>
<td>Rare</td>
</tr>
<tr>
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<td>F</td>
<td>CPS/GTC</td>
<td>33</td>
<td>2</td>
<td>0</td>
<td>CBZ/excise</td>
<td>Rare</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>CPS/GTC</td>
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<td>1</td>
<td>CBZ</td>
<td>Rare</td>
</tr>
<tr>
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<td>M</td>
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<td>0</td>
<td>CBZ</td>
<td>?</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>Episodic dysphasia*</td>
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<td>0</td>
<td>CBZ</td>
<td>?</td>
</tr>
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<td>M</td>
<td>CPS</td>
<td>20</td>
<td>2 days</td>
<td>0.5</td>
<td>CBZ</td>
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*Additional migraine; PHY = phenytoin; VAL = valproate; CBZ = carbamazepine; PHE = phenobarbitaline.

Table 2  Investigations for each patient with epilepsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>CT</th>
<th>MRI</th>
<th>Angiogram</th>
<th>Histology</th>
<th>EEG</th>
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<tbody>
<tr>
<td>1</td>
<td>L temporal calcification</td>
<td>Multiple cavernomas</td>
<td>Normal</td>
<td>ND</td>
<td>L temporal slow waves</td>
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<tr>
<td>2</td>
<td>L temporal calcification</td>
<td>Multiple cavernomas</td>
<td>ND</td>
<td>L parietal vascularity</td>
<td>L temporal slow waves</td>
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<tr>
<td>3</td>
<td>L temporal calcification</td>
<td>L frontal cavernoma</td>
<td>Normal</td>
<td>ND</td>
<td>L temporal slow waves</td>
</tr>
<tr>
<td>4</td>
<td>R parietal calcification</td>
<td>R parietal cavernoma</td>
<td>Normal</td>
<td>ND</td>
<td>Generalised slow waves</td>
</tr>
<tr>
<td>5</td>
<td>L temporal calcification</td>
<td>L temporal cavernoma</td>
<td>Normal</td>
<td>ND</td>
<td>L temporal slow waves</td>
</tr>
<tr>
<td>7</td>
<td>L temporal calcification</td>
<td>L temporal cavernoma</td>
<td>ND</td>
<td>ND</td>
<td>L temporal epileptiform</td>
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<td>10</td>
<td>R occipital calcification</td>
<td>R occipital cavernoma</td>
<td>Normal</td>
<td>ND</td>
<td>R slow waves</td>
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<tr>
<td>11</td>
<td>Unavailable</td>
<td></td>
<td>ND</td>
<td>ND</td>
<td>R temporal epileptiform</td>
</tr>
<tr>
<td>12</td>
<td>R temporal calcification</td>
<td>R temporal cavernoma</td>
<td>Normal</td>
<td>ND</td>
<td>R temporal epileptiform</td>
</tr>
<tr>
<td>13</td>
<td>R temporal calcification</td>
<td>R temporal cavernoma</td>
<td>ND</td>
<td>ND</td>
<td>R temporal epileptiform</td>
</tr>
<tr>
<td>14</td>
<td>L subarachnoid cyst</td>
<td>L parietal cavernoma</td>
<td>Normal</td>
<td>ND</td>
<td>Normal</td>
</tr>
<tr>
<td>15</td>
<td>L parietal calcification</td>
<td>L parietal cavernoma</td>
<td>Normal</td>
<td>ND</td>
<td>Normal</td>
</tr>
<tr>
<td>16</td>
<td>L frontal calcification</td>
<td>L frontal cavernoma</td>
<td>ND</td>
<td>ND</td>
<td>L frontal slow waves</td>
</tr>
</tbody>
</table>

ND = No data.

who underwent resection (figure 1). CT was performed in all cases, and in all but patients 8 and 14 revealed the symptomatic lesion. CT suggested a low grade neoplasm in patients 1-4, 9 and 16. Patients 1 and 2 had multiple cavernomas on MRI, although initial CT scanning demonstrated only 1 lesion. Cavernoma was not definitively diagnosed by CT in any case. Angiography was performed in 10 patients and was normal in all but case 2, where a possible tumour circulation was thought to be indicative of a meningioma. Focal electroencephalographic abnormalities were generally localised to the region of the single or largest cavernoma.

Thirteen patients presented with epilepsy which was longstanding in 10. Successful management with anti-epileptic drugs was achieved in all but patient 5. Seizures have been abolished in patients 3 and 7 and are rare (less than one or two a year) in cases 1, 2, 4, 11 and 13. In Australia, an unprovoked seizure in such patients results in the suspension of the driver’s licence for a period of three to six months. All patients with occasional seizures therefore faced infrequent periods when they could not drive for up to six months, but this was not sufficient to prompt consideration of excision, as all patients were able to remain in employment and maintain normal personal and family lives. Six patients were controlled on carbamazepine alone and one on carbamazepine and phenytoin without significant
Table 3 Clinical details of each patient without epilepsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Presenting complaint</th>
<th>Age (years)</th>
<th>Time at diagnosis (years)</th>
<th>Follow up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>F</td>
<td>Incidental</td>
<td>ND</td>
<td>9</td>
<td>1</td>
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<td>F</td>
<td>Brainstem haemorrhage</td>
<td>33</td>
<td>0</td>
<td>0-25</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Brainstem haemorrhage</td>
<td>50</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

ND = No data.

change to their regime over the time since diagnosis. Patient 10 responded poorly to both sodium valproate and carbamazepine and has recently started phenytoin but its efficacy, as yet, is unknown. Patient 11 was allergic to both phenytoin and carbamazepine, but obtained good control with sodium valproate and phenobarbital. Four patients (10, 14-16) have had too short a follow up to allow an accurate estimation of seizure control. Patient 5 required excision of the lesion because of refractory epilepsy and the presence of a cavernoma was confirmed. Patient 12 presented with epilepsy of two years standing and the cavernoma was excised as prophylaxis against haemorrhage although she had had no history consistent with previous symptomatic haemorrhage. Complete seizure control was obtained with carbamazepine before surgery. She has yet to be followed up postoperatively.

Patient 6 remains asymptomatic after 10 years follow up. The lesion was found unexpectedly after CT to investigate mild mental retardation and a personality disorder. She has never received antiepileptic medications.

Two patients presented with haemorrhage secondary to a brainstem cavernoma and both have been managed conservatively because of the site of the lesion. Patient 8 survived the initial haemorrhage with severe residual deficits and has had no further episodes. Patient 9 suffered a transient neurological episode four years before presentation with three months of progressively worsening bulbar dysfunction and a hemiparesis. Serial CT scans showed a resolving brainstem haemorrhage and he has survived with progressively worsening deficits for a further three years.

The clinical and other details are outlined in tables 1–4.

Asymptomatic haemorrhage and epilepsy
None of the 13 patients with epilepsy had had symptomatic haemorrhages, even though most had been symptomatic for many years. In 11 of these 13 and in the sole patient with an asymptomatic cavernoma, MRI demonstrated a past haemorrhage or haemorrhages that had presumably been asymptomatic or manifest only as seizures. Two patients presented within 72 hours of their first seizure, but MRI demonstrated haemosiderin and calcification indicative of definite asymptomatic haemorrhage in the past in both.

Case histories
CASE 1
At 14 years of age, this otherwise well male developed complex partial seizures (CPS) and presented three years later with an average of one seizure per month. A CT scan showed a left temporal lesion thought to be an oligodendroglioma. An EEG showed a left temporal slow wave focus and he was started on phenytoin and carbamazepine with good control being achieved. Eleven years later he suffered a flurry of seizures and repeat CT and MRI showed multiple cavernomas (figure 2). Neurological examination remained essentially normal. Continued carbamazepine and phenytoin has maintained excellent control with only

Table 4 Investigations for the patients without epilepsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>CT</th>
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<th>EEG</th>
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</thead>
<tbody>
<tr>
<td>6</td>
<td>L frontal calcification</td>
<td>L frontal cavernoma</td>
<td>Normal</td>
<td>Generalised slow waves</td>
</tr>
<tr>
<td>8</td>
<td>Brainstem haemorrhage</td>
<td>Cerbellar cavernoma</td>
<td>Normal</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>Brainstem haemorrhage/calcification</td>
<td>Brainstem cavernoma</td>
<td>Normal</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND = No data.
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CASE 2

At the age of 44, this previously well male developed CPS and presented 10 years later. He suffered occasional CPS whilst on carbamazepine. An EEG showed a left temporal slow wave focus and a CT scan was thought to show a left temporal meningioma. MRI performed seven years later showed multiple cavernomas and multiple lacunes, but no meningioma or neoplasm (figure 3).

Figure 3 (A) Axial T1 weighted (TR SE 2560; TE 25 rms) and (B) axial T2 weighted (TR SE 2560; TE 100 rms) MRI scans from patient 2 showing left temporal cavernoma with variable, central signal intensity and peripheral low intensity and multiple small cavernomas.

Figure 4 (A) Axial, non-contrast CT scan showing calcified left frontal lesion and (B) axial T2 weighted (TR SE 2310; TE 25 rms) MRI scan from patient 3 showing heterogeneous signal intensity centrally and a rim of low intensity at the periphery.
CASE 3
This previously well 48 year old woman suffered three nocturnal generalised seizures over three years. An EEG showed a left temporal epileptiform focus and serial CT scans showed an unchanging left frontal lesion. She was started on carbamazepine and has remained free of seizures. MRI performed 11 years after her first seizure showed a cavernous angioma (figure 4).

Discussion
In this series of 16 patients, 81% presented with epilepsy, two (12.5%) presented with brainstem haemorrhage and one was asymptomatic. The average duration of epilepsy before diagnosis was 5.3 years; three patients had had epilepsy for more than 10 years and eight for more than three years. No patient with epilepsy suffered any of the other complications of cavernomas and only one required resection for refractory seizures. As our MRI scanner services the entire state, and is used by all neurologists and neurosurgeons, we believe that this series accurately represents all or most cavernomas presenting as epilepsy during the time of review.

Previous series have found that cavernomas present as epilepsy in 34-70% of cases, with the remainder presenting as a mass lesion or with an intracranial haemorrhage. In this series 81% presented with epilepsy and of these 13, all but one suffered CPS with or without secondary generalisation. The frequency of those presenting with epilepsy is somewhat higher than in other series, possibly reflecting our entry criterion of MRI diagnosis, whereas earlier series used only CT. Others have noted a predominance of temporal lobe lesions, but this has not been invariable. We found cavernomas to occur in the temporal lobes in most of our patients. Two of our patients had multiple cavernomas and both suffered from epilepsy that was apparently caused by one angioma only. Multiple cavernous angiomas have been documented in a minority of cases in other series.

Recent haemorrhage, as shown by the presence of haemosiderin, has been previously thought common. Recurrent symptomatic haemorrhages have also been documented, but the incidence of subsequent symptomatic haemorrhage in those presenting with epilepsy, a mass lesion or cerebral haemorrhage remains unknown. A necropsy study found that all 22 patients with symptomatic cavernomas had epilepsy, but that only three had had symptomatic haemorrhages, one presented as a mass lesion and 12 had stable neurological deficits. Sixteen of these 22 had evidence of old blood, suggesting that asymptomatic haemorrhage is both common and benign in those with epilepsy. A review of the literature noted that only a few of those suffering a symptomatic cerebral haemorrhage had a history consistent with epilepsy and noted that “the role of surgery in preventing future haemorrhage in patients with seizures can only be speculated”. Asymptomatic cavernomas may also show evidence of past bleeding at necropsy.

Long-standing epilepsy unaccompanied by symptomatic haemorrhage has been noted before. These findings accord with our experience that symptomatic haemorrhage is uncommon in patients presenting with epilepsy only.

Cavernomas had customarily been resected without regard to the presenting complaint in many series. Follow up periods range from being unstated to years. The outcome has generally been stated as good if the frequency of seizures has been reduced, but no series seen by us adequately documented post-operative seizure control, continued use of anti-epileptic drugs ranged from 15-71% and follow up was often less than five years. Evidence that excision of symptomatic cavernomas improves seizure control is lacking despite claims that surgery was generally beneficial.

The absence of supratentorial cavernomas presenting with cerebral haemorrhage in this series may reflect our entry criterion requiring diagnosis by MRI. Cavernomas presenting with haemorrhage may be lethal or resected after an initial CT scan only. Such cases are not included in this series because of lack of systematic access to necropsy and pathology data and their incidence in our community is unknown.

Conclusion
Cavernomas may be symptomatic as epilepsy, intracranial haemorrhage or a mass lesion. Asymptomatic cases occur, but their incidence remains unknown and will be underestimated in clinical series of symptomatic patients. Excision has been widely practised regardless of spontaneous resolution although its efficacy is unknown. In our experience, most patients with epilepsy attain excellent seizure control with anti-epileptic medications. No patient with epilepsy suffered from symptomatic haemorrhage or progressive neurological deficits, which appear to be rare in those presenting with seizures. Asymptomatic and apparently benign haemorrhage, as shown by MRI, is common. In this series only one patient required excision as treatment for refractory epilepsy.

We found no evidence for excision of cavernomas presenting as epilepsy on the grounds of either prophylaxis against haemorrhage, or for improved seizure control in all but refractory epilepsy. We recommend that resection of those cavernous angiomas manifesting as epilepsy alone be considered only if an adequate trial of anti-epileptic drugs fails. Excision of accessible, supratentorial cavernomas presenting with a single or recurrent cerebral haemorrhage or haemorrhages is a valid, although unproven, treatment where surgery is unlikely to increase the patient’s disability.

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