Clinical Associations and Causes of Convexity Subarachnoid Hemorrhage

Ashan Khurram, FRACP; Timothy Kleinig, PhD; James Leyden, FRACP

Background and Purpose—It has been previously found noted that ≈15% to 20% of subarachnoid hemorrhage (SAH) is nonaneurysmal. Nontraumatic convexity SAH (cSAH) is increasingly recognized. Data concerning incidence and associations are scant.

Methods—We identified all SAH-coded cases from South Australian public hospitals between January 2005 and July 2011. Electronic discharge summaries were reviewed, and cases of cSAH were ascertained. Clinical and radiological features were recorded, and pathogenesis was assigned.

Results—Of 742 cases with SAH, 41 (6%) cases were cSAH, giving a minimum population annual incidence of 5.1 per million (95% confidence interval, 3.7–7.0). Median age was 70 years (interquartile range, 48–79). Commonest causes were cerebral amyloid angiopathy (39%), reversible cerebral vasoconstriction syndrome (17%), cerebral venous sinus thrombosis (10%), large-vessel stenotic atherosclerosis (10%), and posterior reversible encephalopathy syndrome (5%). No cause was identified in 20% (mostly elderly patients with incomplete evaluation). Most (63%) presented with transient neurological symptoms. Many (49%) were misdiagnosed as transient ischemic attacks and treated inappropriately with antithrombotics.

Conclusions—cSAH comprises a significant proportion of SAH. Commonest causes are cerebral amyloid angiopathy in the elderly and reversible cerebral vasoconstriction syndrome in the young, but differential diagnosis is broad. Misdiagnosis is common and leads to potentially harmful treatments. (Stroke. 2014;45:00-00.)

Key Words: basal ganglia cerebrovascular disease ■ hemorrhagic disorders ■ stroke ■ subarachnoid hemorrhage

Nontraumatic convexity subarachnoid hemorrhage (cSAH) is a poorly characterized but increasingly recognized form of nonaneurysmal SAH. It has diverse causes, most commonly reversible cerebral vasoconstriction syndrome (RCVS) and cerebral amyloid angiopathy (CAA).1 Patients usually present either with pathogenesis-related symptoms (eg, headache in RCVS) or with transient focal neurological symptoms (TFNS).

The 3 largest case series published comprise 29,3 30,2 and 47 patients (the latter purely RCVS). Incidence, clinical features, causes, and misdiagnosis rates remain unclear. Therefore, we performed this study to clarify these features.

Methods
All cases were identified with a primary International Classification of Diseases, Tenth Revision, SAH diagnosis from Adelaide public hospitals (population, 1.23 million) between January 2005 and July 2011. Adelaide is of relatively homogenous ethnicity (90% European, 7% Asian/Indian, and 2% indigenous.) Ascertainment was restricted to public hospitals because a recent Adelaide population–based stroke incidence study suggested all patients with SAH presented publically.4 Traumatic hemorrhage was excluded. SAHs were subclassified. Five incorrectly coded cSAH cases seen by the authors were included (4 cases personally seen were correctly coded).

Results
Of 1423 cases with SAH that were identified, 792 cases had electronic discharge summaries. Fifty cases were excluded because of inaccurate coding, leaving 742 cases (Table). Forty-one cases with cSAH were identified (6%). This represented a minimum attack rate of 5.1 per million/y (95% confidence interval, 3.7–7.0).

Demographic features are detailed in Table I in the online-only Data Supplement. Median age was 70 years (interquartile range, 48–79). Males and females were equally affected. Eleven (27%) cases had a background history of migraine, and 6 (15%) cases had aura.
Table. Proportional SAH Subcategory Frequency

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysmal</td>
<td>471 (63)</td>
</tr>
<tr>
<td>Extension from intracerebral or subdural hemorrhage</td>
<td>81 (11)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>61 (8)</td>
</tr>
<tr>
<td>Basal idiopathic</td>
<td>50 (7)</td>
</tr>
<tr>
<td>Perimesencephalic</td>
<td>23 (3)</td>
</tr>
<tr>
<td>Pericerebellar idiopathic</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Intracranial malignancy related</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Ischemic stroke transformation</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Idiopathic xanthochromia</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Convexity SAH</td>
<td>41 (6)</td>
</tr>
<tr>
<td>CAA</td>
<td>16 (39)</td>
</tr>
<tr>
<td>RCVS</td>
<td>7 (17)</td>
</tr>
<tr>
<td>CVST</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Vascular stenoses</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Posterior reversible encephalopathy syndrome</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>8 (19)</td>
</tr>
</tbody>
</table>

CAA indicates cerebral amyloid angiopathy; CVST, cerebral venous sinus thrombosis; RCVS, reversible cerebral vasoconstriction syndrome; and SAH, subarachnoid hemorrhage.

Twenty-seven (66%) patients were taking antithrombotics (20 antiplatelets and 7 anticoagulants). In patients with probable CAA, the proportion was 81% (11 antiplatelets 2 anticoagulants). Fourteen (34%) patients were treated previously with statins. Eight patients were taking selective serotonin reuptake inhibitors (3/9 with RCVS/posterior reversible encephalopathy syndrome). One patient with RCVS used illicit drugs, and 2 patients used licit sympathomimetics.

Clinical Features
Most presented with a combination of symptoms (Table II in the online-only Data Supplement). Twenty-seven (66%) patients presented with TFNS, more commonly if >60 years old (22/26 versus 5/15; relative risk, 2.8 [95% confidence interval, 1.2–6.7]). Eighteen patients reported mixed symptoms (varied combinations of motor, sensory, speech, or visual deficits), 4 pure motor symptoms, 2 pure sensory, 1 pure visual, and 2 patients reported isolated facial droop. Most (20/27) patients reported slow evolution of focal symptoms during 5 to 20 minutes. Most (18/27) patients had >1 episode (maximum of 9). Maximum time-course of TFNS recurrence was 90 days.

Twenty (49%) patients experienced some form of headache, most patients were <60 years old (14/20). In 12 patients, headache was thunderclap in onset (10/14 <60 years old, 2/6 >60 years old).

Seven patients had generalized seizures. Four patients (all >60 years old) were diagnosed with partial seizures; however, on retrospective review, events were more consistent with TFNS.

Radiology Findings
Thirty-nine patients (95%) initially underwent computed tomographic neuroimaging. The remaining 2 patients underwent MRI. Subsequently, MRI was performed on 33 patients. In total, 22 patients (54%) received gradient echo or susceptibility weighted imaging sequences. Vessel imaging was performed in 34 patients. Findings are detailed in Table III in the online-only Data Supplement. The most common location for cSAH was the central sulcus (n=19 [46%]). More patients with central sulcus cSAH presented with TFNS (19/19) than patients with hemorrhage elsewhere (odds ratio, 66.5 [95% confidence interval, 3.5–1249]).

Pathogenesis
Probable CAA was the commonest cause of cSAH (16/41 cases; Table; Figure). The second commonest cause was RCVS (7/41). Five definite cases had normal follow-up angiography, and 2 probable cases had classical thunderclap headache presentation, 1 case after intravenous amphetamines, with symptom resolution after nimodipine without immunosuppression. Tight atherosclerotic stenosis (n=4), cerebral venous sinus thrombosis (n=4), and posterior reversible encephalopathy syndrome (n=2) were also evident in multiple cases. All patients with CAA were ≥65 years old. All patients with RCVS and posterior reversible encephalopathy syndrome were <60 years old. Cerebral venous sinus thrombosis and stenosis-related cSAH straddled this age dichotomy.

Figure. Causes of convexity subarachnoid hemorrhage (cSAH). A, Axial gradient echo imaging of patient with recurrent sensorimotor events demonstrating acute (arrow) and chronic cSAH and 2 cortical microbleeds, consistent with CAA. B, Digital subtraction angiography from a patient presenting with thunderclap headache and left frontal cSAH demonstrating diffuse vasoconstriction (arrow). C, Axial computed tomography (CT) demonstrating bilateral cSAH as well as hyperdensity within the sagittal sinus consistent with acute thrombosis. D, Reconstructed CT angiography from a patient with right-sided cSAH demonstrating severe atherosclerotic carotid origin stenosis.
Pathogenesis remained undetermined in 8 patients (20%), 7 patients were >66 years old (none fully investigated).

Twenty patients (49%, all with TFNS) were initially misdiagnosed with transient ischemic attack. In all, preexisting antithrombotic therapy was inappropriately escalated or commenced. In 14 (34%) patients, subsequent imaging suggested worsening cSAH.

**Discussion**

To our knowledge, we report the clinical association and causes of cSAH in the largest mixed pathogenesis case series. We give the first estimate of population incidence. The overall conclusions of our study mirror previous reports. 1-3 cSAH represents a significant SAH subcategory (6% versus 7% reported previously). 4 CAA is the commonest cause in patients >60 years old, and RCVS in those <60 years old. Presentations are distinct, the former with slowly evolving TFNS, the latter usually with thunderclap headache (but sometimes rapid onset focal neurological deficits or seizures).

In contrast with the series of Kumar et al., 1 our commonest presenting complaint was TFNS (66%) not headache (62%), perhaps reflecting a lower RCVS proportion and higher median age. In addition to CAA and RCVS, our study also documented multiple cases with posterior reversible encephalopathy syndrome, cerebral venous sinus thrombosis, and parent vessel stenosis (Figure).

Most patients presenting with TFNS (22 of 27) were >60 years old. Sixteen patients had probable CAA. The remaining 6 patients were possible CAA because they were incompletely investigated. The central sulcus seems to be an area particularly prone to cSAH-induced TFNS. We confirmed previous reports that TFNS are commonly misdiagnosed as transient ischemic attacks. 8 This misdiagnosis (particular as crescendo transient ischemic attacks) may lead to iatrogenic bleeding risk and (if epilepsy is misdiagnosed) unwarranted licensing restrictions.

Our study demonstrated a minimum population incidence of 5.1 per million/year. This is most likely an underestimate because of several study limitations. First, our review was retrospective, lacking characteristics of an ideal incidence study. 9 Second, in several cases, cSAH was subtle and initially missed, suggesting many cases of cSAH may remain undiagnosed. Finally, only publicly admitted cases primarily coded as SAH with available electronic records were reviewed. Coding is often inaccurate; 6% were not actually SAH; and only 4/9 patients with cSAH seen by the authors in this time frame were coded correctly. Cases (especially of CAA-related TFNS) may not be investigated or not seek medical attention at all. Therefore, true cSAH incidence is probably at least double our estimate. An ideal unbiased cSAH incidence study would require comprehensive, prospective, expert, blinded neuroimaging review of a large heavily investigated population during several years.

In conclusion, nontraumatic cSAH occurs relatively commonly. CAA and RCVS are most frequent causes. Increased awareness will prevent misdiagnosis as transient ischemic attack (or seizures) and prevent potentially harmful treatment.

**Disclosures**

None.

**References**

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Supplementary Appendix

Clinical associations and causes of convexity sub-arachnoid haemorrhage.

Supplementary Table I
Background features and preceding medication use

Supplementary Table II
Clinical Features

Supplementary Table III
Radiological Features
Supplementary table I: Background features and preceding medication use

<table>
<thead>
<tr>
<th></th>
<th>N (%) unless indicated</th>
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<tbody>
<tr>
<td>Age</td>
<td>70 years(IQR 48-78)</td>
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<tr>
<td>Male sex</td>
<td>19 (46)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (59)</td>
</tr>
<tr>
<td>Migraine</td>
<td>11 (27)</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>20 (49)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Statins</td>
<td>14 (34)</td>
</tr>
<tr>
<td>SSRI</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Sympathomimetic</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
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IQR=interquartile range, SSRI=selective serotonin reuptake inhibitors
**Supplementary table II: Clinical Features**

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>n</th>
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<tr>
<td>TFNS</td>
<td></td>
<td></td>
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<tr>
<td>Mixed</td>
<td>18</td>
<td>44</td>
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<tr>
<td>Pure Motor</td>
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<td>8</td>
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<tr>
<td>Pure Sensory</td>
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<td>5</td>
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<tr>
<td>Isolated facial palsy</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Pure Visual</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pure Speech</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Generalised seizure</td>
<td>7</td>
<td>17</td>
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<tr>
<td>Diagnosed partial seizure*</td>
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<td>9</td>
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<tr>
<td>Previous epilepsy</td>
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<td>0</td>
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<tr>
<td>OTHER</td>
<td></td>
<td></td>
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<tr>
<td>Visual disturbance</td>
<td>7</td>
<td>22</td>
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<tr>
<td>Flashing Lights</td>
<td>5</td>
<td>12</td>
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<tr>
<td>Blurred Vision</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Other visual</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Confusion</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
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* In retrospect more consistent with TFNS (i.e. aura-like progression of symptoms)
### Supplementary table III Radiological Features

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% age</th>
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<tbody>
<tr>
<td><strong>Haemorrhage Location</strong></td>
<td></td>
<td></td>
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<tr>
<td>Central sulcus</td>
<td>19</td>
<td>46</td>
</tr>
<tr>
<td><em>Other</em></td>
<td>22</td>
<td>54</td>
</tr>
<tr>
<td>Right sided</td>
<td>24</td>
<td>59</td>
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<tr>
<td>Left Sided</td>
<td>14</td>
<td>34</td>
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<tr>
<td>Bilateral</td>
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<td>7</td>
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<tr>
<td><strong>Microbleeds</strong></td>
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<td></td>
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<tr>
<td>Superficial</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>Superficial + deep</td>
<td>1</td>
<td>2</td>
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<tr>
<td><strong>Macrobleeds</strong></td>
<td>3</td>
<td>7</td>
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<tr>
<td><strong>Superficial Siderosis</strong></td>
<td>13</td>
<td>32</td>
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<tr>
<td><strong>Vasoconstriction</strong></td>
<td>7</td>
<td>17</td>
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<tr>
<td><strong>Atherosclerotic Stenosis</strong></td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Venous Sinus Thrombosis</strong></td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Reversible Leucoencephalopathy</strong></td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>Acute diffusion weighted +ve lesions</strong></td>
<td>5</td>
<td>12</td>
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<tr>
<td><strong>White Matter Disease</strong></td>
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<td></td>
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<tr>
<td>Grade 0</td>
<td>20</td>
<td>49</td>
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<td>Grade 3</td>
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Reference
円蓋部くも膜下出血の臨床的関連性と原因
Clinical Associations and Causes of Convexity Subarachnoid Hemorrhage

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背景および目的：くも膜下出血（SAH）の約15〜20%は非動脈瘤性であることが過去の研究から明らかになっている。非外傷性円蓋部SAH（cSAH）の認識が高まりつつあるが、発生率および臨床的関連性に関するデータはまだ十分である。

方法：2005年1月〜2011年7月までの期間で、南オーストラリアの公立病院においてSAHと診断された症例をすべて特定した。電子カルテの退院サマリーを検討してcSAH症例を確認し、臨床的特徴および放射線学的特徴を記録し、病因を特定した。

結果：SAH患者742例中41例（6%）がcSAHで、最低人口年間発生率は100万人に5.1人であった（95%信頼区間（CI）：3.7〜7.0）。年齢中央値は70歳であった（四分位間隔範囲：48〜79）。原因となった疾患は、脳アミロイドアミロイドアンギオパチー（39%）が最も多く、可逆性脳管脛性症候群（17%）、脳静脈洞血栓症（10%）、主幹動脈のアテローム性動脈硬化による狭窄（10%）、および後部可逆性脳症候群（5%）が続いた。20%は原因不明であった（大多数が高齢者で評価が完全に不可能であった）。大半の患者（63%）が一過性の神経症状を呈し、多くの患者（49%）が一過性脳虚血発作と誤診され抗血栓療法による不適切な治療を受けていた。

結論：cSAHがSAHのほとんどを占めている。最も多い原因は、高齢患者では脳アミロイドアミロイドアンギオパチー、若年患者では可逆性脳管脛性症候群であったが、鑑別診断が広範である。診断が遅く、そのため潜在的に有害な治療が行われている可能性がある。

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