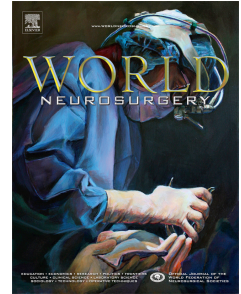


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“Sentinel seizure” as a warning sign preceding fatal rupture of a giant middle cerebral artery aneurysm

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1 **“Sentinel seizure” as a warning sign preceding fatal rupture of a giant**  
2 **middle cerebral artery aneurysm**

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21 **Keywords:** aneurysm, sentinel headache, seizure, and subarachnoid hemorrhage

22  
23 **Short title:** “Sentinel seizure” preceding aneurysmal rupture

24  
25 **Abbreviations:** CT = computed tomography; MCA = middle cerebral artery; SAH =  
26 subarachnoid hemorrhage; SH = sentinel headache.

27  
28 **Ethical standards and patient consent:** This study was approved by the Ethical Committee  
29 of Bern (Kantonale Ethikkommission, KEK, Bern, Switzerland), the Swiss Ethic Committee  
30 on research involving humans. The study has been performed in accordance with the ethical  
31 standards laid down in the 1964 Declaration of Helsinki and its later amendments.

32

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45 **ABSTRACT:**

46 **Background:** Sentinel headache is a well-known warning sign preceding subarachnoid  
47 hemorrhage (SAH) due to rupture of an intracranial aneurysm. New-onset seizure or “sentinel  
48 seizure” preceding aneurysmal SAH, however, is uncommon.

49 **Case Description:** We report on a 51-year-old man who presented with a new-onset seizure.

50 Diagnostic work-up revealed a giant middle cerebral artery aneurysm without evidence of  
51 subarachnoid or intracerebral hemorrhage. Anti-epileptic therapy was initiated, elective  
52 diagnostic angiography and subsequent treatment was scheduled and the patient discharged  
53 home. Four days later, he suddenly lost consciousness and subsequently died due to a  
54 massive aneurysmal SAH.

55 **Conclusions:** As with sentinel headache, new-onset seizures in patients with unruptured  
56 intracranial aneurysms might prompt immediate treatment to prevent imminent SAH with its  
57 subsequent high morbidity and mortality.

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**67 BACKGROUND**

68 Sentinel headache (SH) is a well-known warning sign for aneurysmal subarachnoid  
69 hemorrhage (SAH).<sup>1</sup> SH may precede aneurysmal rupture by hours to weeks. Its incidence  
70 ranges from 10% to 60% of all patients eventually admitted with aneurysmal SAH.<sup>2</sup> Mortality  
71 is high, given that SH is strongly related to a higher risk of aneurysmal rupture.<sup>3, 4</sup> Hence,  
72 distinguishing SH from innocuous headache is essential for preventing a fatal outcome. New-  
73 onset seizure or “sentinel seizure” has not previously been described as a warning sign of  
74 aneurysmal rupture and SAH, although the mechanisms might be similar to those reported in  
75 SH.

**76 CASE DESCRIPTION**

77 A previously healthy 51-year-old man with a history of migraine was referred to the  
78 emergency department due to a new-onset secondary generalized tonic-clonic seizure lasting  
79 for 10 minutes. No history of hypertension was recorded. Initial blood pressure at presentation  
80 was 148/80 mmHg, which had dropped to 125/70 mmHg at first discharge. No injuries were  
81 detected upon clinical examination apart from tongue bites. A non-enhanced cerebral  
82 computed tomography (CT) scan showed a hyperdensity measuring 27 × 25 × 26 mm, at the  
83 left M1 trunk of the middle cerebral artery (MCA). There was no distinct radiological  
84 evidence of SAH, either in the non-enhanced cerebral computed tomography scan (CT scan,  
85 Fig. 1A), or in the magnetic resonance imaging using fluid attenuated inversion recovery  
86 (FLAIR) of the magnetic resonance images (Fig. 1B) at the time of seizure, which yields a  
87 higher detection rate for subarachnoid hemorrhage (SAH) than CT alone.<sup>2, 5</sup> However, the  
88 perfused portion of the aneurysm showed an irregular shape in the CT-angiographic  
89 reconstruction (Fig. 1A, insert) – a known risk factor for aneurysmal rupture.<sup>6</sup> The  
90 subsequent magnetic resonance angiography (MRA) revealed a giant, partially thrombosed  
91 aneurysm arising at the junction of the M1 and M2 segments of the left MCA (Fig. 1C).  
92 Moreover, there was no evidence of perianeurysmal edema at the time of the seizure (Fig.  
93 1B), a predictive sign of aneurysmal rupture including risk for immediate rupture.<sup>7</sup>  
94 The subsequent magnetic resonance angiography (MRA) revealed a giant, partially  
95 thrombosed aneurysm arising at the junction of the M1 and M2 segments of the left MCA  
96 (Fig. 1C). No xanthochromia of the cerebrospinal fluid (CSF) was detected 12 hours  
97 following the epileptic seizure. Past medical history and family history of intracranial  
98 aneurysms or SAH were negative. Neurological examination was normal. Anti-epileptic  
99 therapy with levetiracetam was initiated. The patient was scheduled for elective diagnostic  
100

101 angiography with subsequent treatment and was discharged home. Four days later, his wife  
102 found him comatose. Upon arrival at the emergency department, he presented with bilaterally  
103 fixed, dilated pupils. CT revealed acute aneurysmal rupture with massive SAH and left  
104 temporal and intraventricular hemorrhage, as well as midline shift, uncal herniation and  
105 hypodensity of the brain stem (Fig. 1D and E). CT angiography showed circulatory arrest  
106 (Fig. 1F), and the diagnosis of brain death was established by clinical criteria.

## 108 DISCUSSION

109 To the best of our knowledge, new-onset seizures or “sentinel seizures” have not been  
110 described as a warning sign of aneurysmal rupture or SAH. A few cases of unruptured  
111 aneurysms associated with epilepsy have been reported; these were most likely related to  
112 subclinical hemorrhages,<sup>8</sup> presence of thrombus<sup>9, 10</sup> or aneurysm location related to the  
113 temporomesial region,<sup>11-13</sup> but none of these aneurysms were related to the index SAH, or  
114 associated with SAH several days following diagnosis. As for SH, warning symptoms may  
115 occur a few hours up to a few months prior to SAH and suggest minor leaks (sentinel bleeds)  
116 or structural changes within the aneurysm wall, mostly characterized by severe headache with  
117 the characteristics of SAH.<sup>2</sup> SH may also precede aneurysmal rupture without any bleeding.<sup>14</sup>  
118 Jea et al. reported on a 48-year-old man suffering from a giant internal carotid artery–  
119 ophthalmic artery aneurysm, who experienced a potential warning bleed with subsequent  
120 visual deterioration but evidence of SAH was absent on imaging scans and upon operative  
121 exploration.<sup>15</sup> It might be plausible that minor leaks, as described in SH, result in cortical  
122 irritation and subsequent seizures. In the present case, the new-onset seizure might have been  
123 provoked by microbleeding in the brain, changes in the aneurysmal wall, or intraaneurysmal  
124 thrombus formation with subsequent cortical irritation- suggested mechanisms described in  
125 patients with unruptured giant aneurysms presenting with seizures.<sup>10, 13</sup> As for cerebral  
126 microbleeding, the absence of subarachnoid blood in the MRI might be due to the  
127 concentration of hemoglobin being below the detection threshold of fluid attenuated inversion  
128 recovery (FLAIR) sequences (Fig. 1B). In fact, FLAIR MRI sequences were only positive in  
129 16.7% of cases where CT findings were negative for SAH that was confirmed by lumbar  
130 puncture.<sup>16</sup> Despite the high sensitivity and specificity of a CT scan plus lumbar puncture in  
131 detecting SAH,<sup>17</sup> negative findings in patients with SH have been described, similar to the  
132 results of our diagnostic work-up in the patient with “sentinel seizures”.<sup>18</sup> The fact that the  
133 patient had suffered from migraine for the past 10 years probably did not contribute to the  
134 higher risk of SAH. A recent meta-analysis concluded that migraine potentially increases the

135 risk of hemorrhagic stroke;<sup>19</sup> however, evidence as to whether there is an increased risk for  
136 SAH in migraineurs remains ambiguous.<sup>20</sup> Similar controversy exists as to whether there is a  
137 higher prevalence of seizures in patients with migraine,<sup>21</sup> and no increased prevalence of SH  
138 in patients with migraine has been described.<sup>22</sup>

139 To sum up, the presence of “sentinel seizures” may act as a warning sign for aneurysmal  
140 SAH, as is known to be the case for SH. Proper identification, decision-making and initiation  
141 of therapy is essential in an attempt to prevent aneurysmal rupture with its subsequent high  
142 morbidity and mortality. The impact of “sentinel seizures” requires further clarification to  
143 confirm its importance as a warning sign preceding aneurysmal SAH and we are aware that  
144 no firm conclusion can be drawn based on one single case report with a seizure episode in the  
145 absence of significant perianeurysmal edema. Nevertheless, we feel that immediate treatment  
146 may be warranted until the significance of this potentially harmful feature becomes clearer.

147

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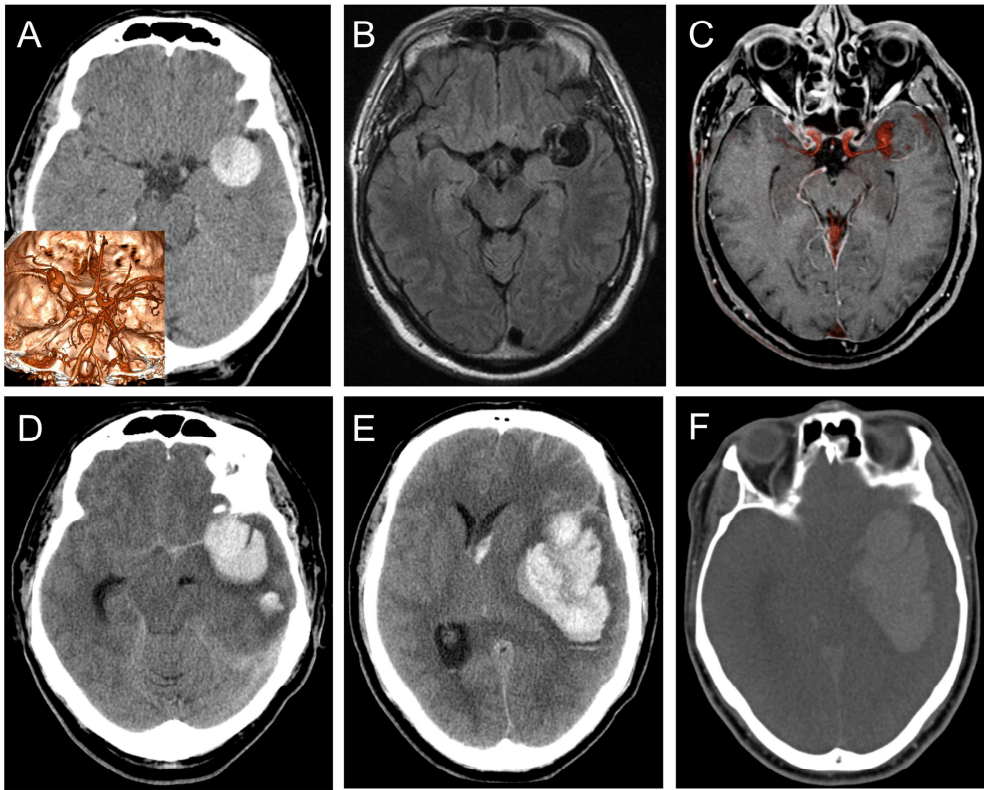
218 **FIGURE AND FIGURE LEGEND:**

219 **FIG 1: Radiological examination before (A–C) and after (D–F) aneurysmal rupture.**

220 **FIG. 1:** Non-enhanced CT scan (A) and CT-angiographic reconstruction of the perfused  
221 portion of the aneurysm (A, insert) and FLAIR MRI (B) showing the giant irregular left-sided  
222 M1/2 aneurysm with no evidence of SAH. MR-Angiography with perfused (red) and  
223 thrombosed (dark) portion of the aneurysm (C). Non-enhanced CT scan demonstrates  
224 extensive SAH with filling of the basilar cisterns and midline shift caused by the ruptured  
225 MCA aneurysm (D), including lobar and intraventricular bleeding (E). In the CT-angiogram,  
226 gray/white matter differentiation is no longer discernible, with no opacification of the  
227 intracranial arteries, while opacification of the superficial temporal arteries on both sides  
228 indicates sufficient contrast injection (F).

229

230



ACCEPTED

- Sentinel headache is a well-known warning sign preceding aneurysmal SAH
- New-onset seizure or “sentinel seizure” (SS) preceding aneurysmal SAH is uncommon
- SS in patients with unruptured aneurysms might prompt immediate treatment

ACCEPTED MANUSCRIPT