Clinical Analysis of Fever, Headache, and Gastrointestinal Symptoms after Endosaccular Coil Embolization in Patients with Unruptured Cerebral Aneurysms—A Study of “Post Coiling Syndrome”

Yu Okuma,1,2 Kenji Sugiu,2 Koji Tokunaga,2 Ayumi Nishida,2 Tomohito Hishikawa,2 Hisakazu Itami,2 Masafumi Hiramatsu,2 and Isao Date2

Objective: Unidentified fever, headache, and gastrointestinal symptoms after endosaccular coil embolization are occasionally observed in patients with unruptured cerebral aneurysms. We defined these symptoms as post coiling syndrome (PCS) and analyzed the clinical risk factors involved.

Methods: We applied the PCS diagnostic criteria based on the scoring of symptoms, which include fever, headache, nausea, and/or vomiting. Thirty-six consecutive patients were included in this retrospective study. Systematic follow-up included clinical and blood examinations.

Results: Based on our criteria, 11 of 36 patients were diagnosed with PCS. Between patients in the PCS group and patients in the non-PCS group, we recognized significant differences in age (63.4 ± 12.5 vs. 53.8 ± 12.9, respectively; p < 0.029) as patient background and in aneurysmal diameter (9.96 ± 4.24 vs. 6.48 ± 3.06, respectively; p < 0.049), aneurysmal volume (242 ± 254 vs. 87.9 ± 70.1, respectively; p < 0.015), total coil length (122 ± 106 vs. 39.1 ± 25.7, respectively; p < 0.0021), and volume embolization ratio as aneurysmal data (41.9 ± 8.1 vs. 30.7 ± 8.5, respectively; p < 0.0019). In addition, we recognized a significant difference in postoperative leukocytosis as an inflammatory factor.

Conclusions: Patient age, aneurysmal diameter, aneurysmal volume, total coil length, and volume embolization may enable the prediction of PCS.

Keywords ▶ post coiling syndrome, unruptured cerebral aneurysms, fever, headache, nausea

Introduction

Endosaccular coil embolization recently became an acceptable method for the occlusion of unruptured cerebral aneurysms.1 Unidentified fever, headache, and gastrointestinal symptoms are occasionally observed after endosaccular coil embolization in patients with unruptured cerebral aneurysms.2-3 Little is known about these symptoms following endosaccular coil embolization.

These clinical symptoms are similar to those of the post-embolization syndrome that is seen in patients who have undergone embolization of the uterine artery, splenic artery, hepatic artery, renal artery, and so on. It has been speculated that these symptoms may be the result of an inflammatory response.4-8

We define these symptoms as post-aneurysmal coiling syndrome (PCS). The purpose of this study is firstly to analyze the clinical risk factors of PCS, and secondly to prevent patients from experiencing PCS.

Materials and Methods

A retrospective study of consecutive patients who underwent coil embolization for unruptured cerebral aneurysms...
between June 2008 and April 2010 at our institution was performed. Our treatment indication for unruptured aneurysm was based on International Study of Unruptured Intracranial Aneurysms (ISUIA) guidelines.

This study included 36 patients (12 men and 24 women) aged 25 to 75 years (mean age: 62 years). Systematic follow-up included clinical and blood examinations. Blood examinations were performed immediately before (<6 h) and after (≥24 h) the procedure, and included investigation of the coagulation fibrinogenolysis system, full blood counts, liver functions, renal functions, inflammatory reactions, and so on.

All intra-aneurysmal embolizations were performed with general anesthesia. All patients who underwent coil embolization have received dual antiplatelet therapy (clopidogrel and aspirin) to prevent thrombotic complications.

We applied the PCS diagnostic criteria based on the scoring of symptoms between 24 h and 48 h after the operation. These criteria include fever (0 = none; 2 = higher than 37.5°C), headache (0 = none; 1 = headache responsive to medication; 2 = headache refractory to medication), and nausea and/or vomiting (0 = none; 1 = nausea; 2 = vomiting). Using our criteria, a diagnosis of PCS can be made with a total score of three points or higher (Table 1).

We excluded patients who had infectious signs, such as pharyngalgia, cough, or abnormal blood culture or lumbar puncture test results, from this retrospective study. Additionally, we excluded patients who had complications during the course of procedures. And we excluded patients who had taken a pain killer before treatment, patients accompanied by other brain lesions, and patients with other combined diseases such as psychosis, autoimmune disease.

Volume embolization ratio was calculated by using the following algebraic equation: volume embolization ratio (%) = (volume of the embolized coil)/(volume of the aneurysm) × 100: volume of the embolized coil = π × (diameter of coil/2)² × length of coil: volume of the aneurysm = 4π/3 × (width/2)² × (length/2) × (height/2)².

Statistical analysis with the Mann–Whitney U test was performed. Positive statistical significance was determined according to a p value of less than .05. Statistical analysis was performed with StatView software (version 5.0).

### Patient background

There was a significant difference in age between patients in the PCS and the non-PCS groups. The mean age was 63.4 in the PCS group and 53.8 in the non-PCS group (p <.05). This finding demonstrates that patients in the PCS group were significantly older than those in the non-PCS group. On the other hand, except for age, there were no significant differences (Table 2).

### Aneurysmal data of the patients

There was a significant difference in the aneurysmal diameter, aneurysmal volume, total coil length, and volume embolization ratio (VER) between the PCS and the non-PCS group. The mean aneurysmal diameter was 9.96 mm in the PCS group and 6.48 mm in the non-PCS group (p <.01). The mean

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**Table 1** The PCS diagnostic criteria

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Lower than 37.5°C</td>
<td>0</td>
</tr>
<tr>
<td>Higher than 37.5°C</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Headache responsive to medication</td>
<td>1</td>
</tr>
<tr>
<td>Headache refractory to medication</td>
<td>2</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
</tbody>
</table>

| Total                           |       |
|                                 |       |

<table>
<thead>
<tr>
<th>Scoring for evaluation of diagnostic criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>Non-PCS</td>
</tr>
<tr>
<td>≥3</td>
<td>PCS</td>
</tr>
</tbody>
</table>

PCS: post coiling syndrome

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**Fig. 1** Pie chart of the PCS diagnostic criteria scoring. PCS: post coiling syndrome

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The aneurysmal volume was 242 mm$^3$ in the PCS group and 87.9 mm$^3$ in the non-PCS group ($p<0.05$). The mean length of the coils was 122 cm in the PCS group and 39.1 cm in the non-PCS group ($p<0.01$). The mean VER was 41.9% in the PCS group and 30.7% in the non-PCS group ($p<0.05$) (Table 3).

There were no significant differences in the total bioactive coil length, ratio of bioactive coil (%), aneurysm location, and adjunctive technique. The mean total bioactive coil (GDC Matrix (Boston Scientific, Fremont, CA, USA) and Cerecyte (Micrus Endovascular, San Jose, CA, USA)) length was 34.6 cm in the PCS group and 13.4 cm in the non-PCS group. The mean ratio of bioactive coil was 44.1% in the PCS group and 39.2% in the non-PCS group. The ratio of posterior circulation in aneurysmal location was 27.3% in the PCS group and 24.0% in the non-PCS group. The ratio of adjunctive technique (% balloon remodeling technique) was 81.8% in the PCS group and 88.0% in the non-PCS group (Table 3, Fig. 2).

This study demonstrated that the aneurysms of the patients in the PCS group were significantly bigger and were more tightly filled with coils than those in the non-PCS group.

**Laboratory data of the patients**

There were no significant differences in preoperative laboratory data. However, there was a significant difference in the postoperative white blood cell (WBC) count between the PCS and the non-PCS group. The mean WBC count was 7660 (/ml) in the PCS group and 6960 (/ml) in the non-PCS group ($p<0.05$). As inflammatory factors, the postoperative WBC count of the PCS group was significantly bigger than...
that of the non-PCS group, despite the fact that there were no significant differences in preoperative C-reactive protein (CRP), WBC count, or postoperative CRP (Table 4).

Operative factors of the patients

There were no significant differences in operative time or contrast medium volume between the PCS group and the non-PCS group (Table 5).

Hospital days after procedure

There was no significant difference in the hospital days after procedure between PCS and non-PCS group. The mean hospital days was as 8.5 (days) in the PCS group, 6.2 (days) in the non-PCS group (Fig. 3).

Discussion

Thus far, post-embolization syndrome (PES) has been defined as a combination of flu-like symptoms, including unidentified fever, headache, nausea, and/or vomiting within the first 24 h to 48 h after embolization of the uterine artery, splenic artery, hepatic artery, renal artery, and so on. This study demonstrated that similar symptoms were observed in PCS, and similar leukocytosis was also observed in PCS (Table 4).

Recent studies have suggested that the etiology of PES is related to an inflammatory process/cascade and tissue ischemia and necrosis although there are some differences in blood flow preservation between PCS and PES. Tissue ischemia and necrosis are not involved in PCS. Conversely, the inflammatory process/cascade is thought to play a more important role in PCS.

It is important to distinguish the clinical course of PCS from other postprocedural complications, such as concurrent infection or cerebral infarction. As such, we excluded patients who had infectious signs or complications due to procedures.

Several *in vitro* and *in vivo* studies have reviewed the impact of general anesthesia on the immune system. Importantly, almost all such studies reported a short-lived and reversible influence on the immune reaction that mostly returned to preoperative values within 24 h. Given this, in our study, we applied the PCS diagnostic criteria based on the scoring of such symptoms between 24 h and 48 h after the operation.

We also suspected that some symptoms were caused by nephropathy induced by the contrast medium and radiation sickness. However, there was no significant difference in operative time and contrast medium volume between the PCS group and the non-PCS group. In addition, there was also no significant difference in the marker of renal function (Table 4).

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**Table 4** Pre/postoperative laboratory data of the patients in the PCS and non-PCS groups

<table>
<thead>
<tr>
<th></th>
<th>Preoperative data</th>
<th>Postoperative data</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCS</td>
<td>non-PCS</td>
<td>PCS</td>
<td>non-PCS</td>
</tr>
<tr>
<td></td>
<td>n = 11</td>
<td>n = 25</td>
<td>n = 11</td>
<td>n = 25</td>
</tr>
<tr>
<td>WBC</td>
<td>5430 ± 1040</td>
<td>4770 ± 1800</td>
<td>0.18</td>
<td>7660 ± 843</td>
</tr>
<tr>
<td>CRP</td>
<td>0.0400 ± 0.0193</td>
<td>0.0546 ± 0.0667</td>
<td>0.62</td>
<td>0.257 ± 0.113</td>
</tr>
<tr>
<td>BUN</td>
<td>13.3 ± 2.17</td>
<td>14.4 ± 6.69</td>
<td>0.62</td>
<td>12.7 ± 5.29</td>
</tr>
<tr>
<td>Cre</td>
<td>0.601 ± 0.0952</td>
<td>1.19 ± 1.94</td>
<td>0.56</td>
<td>0.620 ± 0.120</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± s.d. *p* < 0.05. BUN: blood urea nitrogen; Cre: creatinine; CRP: C-reactive protein; PCS: post coiling syndrome; s.d.: standard deviation; WBC: white blood cell count

**Table 5** Operative time and contrast medium volume of the patients in the PCS and non-PCS groups

<table>
<thead>
<tr>
<th></th>
<th>PCS</th>
<th>non-PCS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 11</td>
<td>n = 25</td>
<td></td>
</tr>
<tr>
<td>Contrast medium (ml)</td>
<td>116 ± 30.0</td>
<td>120 ± 25.4</td>
<td>0.58</td>
</tr>
<tr>
<td>Time (min)</td>
<td>168 ± 30.9</td>
<td>145 ± 48.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>

PCS: post coiling syndrome

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![Fig. 3](journalneuroendovastherapy.com/10/4/19040/fig3.png)
As such, it is evident that PCS is not related to contrast medium or radiation sickness.\textsuperscript{13-15}

The exact cause of these symptoms remains controversial. It is reasonable to consider, however, that the placement of numerous coils into the cerebral artery may cause an inflammatory reaction or dural irritation.\textsuperscript{3,4} The inflammatory response is known to participate in the biological processes of endothelialization. Some studies have reported that the aneurysmal wall becomes disorganized by the invasion of capillaries and fibroblasts that organize the thrombotic material and initiate a foreign body reaction in the neighborhood of the coils after coil embolization.\textsuperscript{16-18} Some studies have also reported that the aneurysmal wall developed multiple bulges after embolization because of the tension of the coil loops.\textsuperscript{19} The mass of the coils would also be expected to have some direct mechanical effect on the adjacent brain. The dramatic alteration in directional blood flow may also contribute to some of the discomfort and/or disorientation. Our study demonstrated that the aneurysms of patients in the PCS group were significantly bigger and were more tightly filled with coils than those of the patients in the non-PCS group (Table 3). These results are consistent with these theories.

The resolution of these symptoms with anti-inflammatory treatment supports this inflammatory theory.\textsuperscript{20,21} To date, pretreatment with steroids may have been of value in attenuating these difficulties, as it limits the unidentified fever, headache, and nausea often noted after embolization. Although bioactive coils are suspected to influence the development of PCS, there was no significant difference, especially in the mean ratio of bioactive coil. And these symptoms disappear within a few days. So that there was no significant difference in the hospital days.

The goal of this study was to identify the procedural variables that could predict the risk of PCS and the extended postprocedural hospitalization after coil embolization. This knowledge may prevent patients from undergoing unnecessary treatment such as antibiotic treatment, steroid treatment, and so on. To the best of our knowledge, this is the first study in regard to PCS.

The limitations of this study are the small number of patients, the lack of prospective data collection, and selection bias. Further study regarding the mechanism of PCS and the criteria of PCS is required in the future. It is also necessary to think about a similarity and difference with PES. Additionally, we plan to examine more data that pertains to the inflammatory reaction, such as the differential white blood count, TNF-\textgreek{a}, Interleukin family, and so on. And in this study, we did not use classification of headaches based on International Headache Society criteria, so we need to use this classification in future studies.

\section*{Conclusion}

We studied symptoms such as unidentified fever, headache, and gastrointestinal symptoms after endosaccular coil embolization in patients with unruptured cerebral aneurysms and defined these symptoms as post-aneurysmal coiling syndrome (PCS). Our study revealed that patient age, aneurysm diameter, aneurysm volume, total coil length, and volume embolization ratio may enable us to predict PCS. Further study regarding the mechanism of PCS is needed.

\section*{Disclosure Statement}

There is no conflict of interest to be disclosed.

\section*{References}


