Occlusive Thromboaortopathy (Takayasu’s Disease): Cervical Arterial Stenoses, Retinal Arterial Pressure, Retinal Microaneurysms and Prognosis

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SUMMARY Eighty-one young Japanese patients with occlusive thromboaortopathy (Takayasu’s disease) were classed into three groups according to the degree and extent of diameter stenosis in the 4 cervical arterial systems, as determined by serial arteriography. Class I was made up of 63 patients with 70% or greater stenosis in less than 3 systems, including 33 patients without systemic hypertension (Class Ia). Class II was made up of 6 patients with 70% or greater stenosis in 3 systems and less than 50% stenosis in the remaining 1, including 5 patients without systemic hypertension (Class IIA). Class III was made up of 12 patients with 70% or greater stenosis in 3 systems and 50% or greater stenosis in 1 system. Ophthalmodynamometric systolic pressure in patients in Class III was significantly lower than that in patients in Class IIA (p < 0.001), but there was no significant difference between patients in Classes Ia and IIA. Microaneurysms and/or arteriovenous anastomoses in the retinal vessels were found in all but one patient in Class III and in only one patient in combined Classes I and II. These results indicate that each of the ophthalmodynamometric values and fundoscopic findings are very helpful in identifying the markedly severe occlusive lesions (Class III) of the 4 cervical arterial systems. In this chronic disease, however, angiography is most useful for evaluation of these severe lesions, to monitor progression from Classes I and II to Class III, in which the prognosis is rather poor.

RELATIONSHIP among cervical arterial stenoses, retinal arterial pressure and retinal vascular changes in occlusive thromboaortopathy (Takayasu’s disease) is not clear. The disease is a chronic inflammatory arteriopathy of unknown origin and the site of occurrence is the aorta and/or its main branches.1,2 Intracranial arteries and the distal segments of the bifurcation of the common carotid arteries and those of the vertebral arteries are usually spared in this disease.3-7 Therefore, these patients appropriately serve as unique subjects for assessment of the influence of gradually developing stenoses in the proximal segments of the aortic arch vessels, as related to retinal arterial pressure and ischemic retinopathy. A severe retinopathy of arteriovenous anastomoses and microaneurysms, a characteristic manifestation of Takayasu’s retinopathy9 is one of the ominous signs in prediction of a poor prognosis in patients with this disease.10,11 Consequently, it is very important to investigate stepwise, the cervical arterial stenoses which cause severe ischemic retinopathy.

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Eighty-one patients with Takayasu’s disease treated by the authors were separated into three classes with special reference to the four cervical arterial stenoses, evidenced by serial aortography. The relationship among the degree and extent of the arterial lesions, ophthalmodynamometric systolic pressure and retinal vascular changes was then analyzed and prognostic and therapeutic implications were discussed.

**Methods**

**Patient Selection**

During the 25 year period from May 1957 to May 1982, a total of 92 Japanese patients with Takayasu’s disease were admitted to the Third Department of Internal Medicine, Kyoto University where the diagnosis of the disease was established. In 81 of the 92, supravalvular and abdominal aortography, ophthalmodynamometry and fundoscopy were performed. The present report concerns these 81 patients, including 8 men. All patients had narrowing or occlusion in some region of the aorta and/or its main branches. According to the location of arterial lesions, three types in the disease were anatomically defined, namely, aortic arch type, descending aorta type and extensive type which means combined aortic arch and descending aorta type.

In the present series, 28 (35%) belonged to the aortic arch type, 51 (63%) to the extensive type combined aortic arch and descending aorta type, and 2 (2%) to the descending aorta type. The average age at the time of onset of symptoms of Takayasu’s disease and at the time of the established diagnosis was 22.1 ± 7.2 (SD) and 31.4 ± 10.4 years, respectively. Each patient was prospectively followed up for observation periods ranging from one month to 18.3 years after the diagnosis, the average being 7.1 ± 4.9 (SD) years.

**Expression of Cervical Arterial Stenoses**

The four courses from the arch of the aorta to the bifurcations of bilateral common carotid arteries and to the distal segments (near the level of the 2nd or 3rd cervical vertebra) of bilateral vertebral arteries were defined as the four cervical arterial systems (4CAS), in the present series. These 4 systems were examined by serial aortography. Grading of stenosis of each cervical arterial system was based on the aortograms and was expressed as a percentage reduction of the original luminal diameter, assessed on the basis of the immediate proximal or distal unininvolved segment. In case of no adjacent normal segment, we used the average diameter of the corresponding segments of normal angiograms in 10 women undergoing aortography for diseases other than Takayasu’s disease. There was no significant difference in the average age between 81 patients in this series and 10 control patients whose average age was 30.2 ± 12.7 (SD) years (t-test). To express the grade in stenosis in one arterial system, the narrowest point was selected. For example, in case of a 70% stenosis at the proximal portion of the left subclavian artery and no stenosis of the ipsilateral vertebral artery, the flow is theoretically affected in the left vertebral artery, and in our study, such is defined as the left vertebral system with a 70% stenosis.

**Patient Classification**

The 81 patients were separated into three classes according to the degree and extent of stenosis in the 4CAS at the time when the diagnosis of the disease was established.

- Class I included 63 patients (78%), 70% or greater stenosis in less than 3 cervical arterial systems. Of the 63, 33 had no systemic hypertension (Class Ia).
- Class II included 6 patients (7%), 70% or greater stenosis in 3 vessel systems and less than 50% stenosis in the remaining one. Of the 6, 5 had no systemic hypertension (Class IIa).
- Class III included 12 patients (15%), 70% or greater stenosis in 3 vessel systems and 50% or greater stenosis in one system. Systemic hypertension was evident in 5 patients. The criteria for evaluation of systemic blood pressure were as previously reported.

**Ophthalmodynamometry**

Retinal arterial pressure was measured using a Müller’s ophthalmodynamometer, according to Bailiart’s method. The values in grams of pressure applied to the sclera were converted into mm Hg by reference to the conversion table for the dynamometer, taking into consideration the intraocular pressure measured with a Schiottz tonometer. To facilitate analysis of the relationship between retinal arterial pressure and other parameters, we made use of a higher value in systolic pressure of the retinal artery in both eyes, measured with the patient in the supine position. Most patients in this series showed no significant difference in bilateral retinal arterial pressure. Ocular fundi of all patients in this series were examined by each one of two ophthalmologists (M.U. and K.A.), who also measured retinal arterial pressure.

Statistical comparisons were made using the one-way analysis of variance (fig. 1) and the chi-square method with Yates correction for continuity (table 1).

**Results**

**Cervical Arterial Stenoses and Retinal Arterial Systolic Pressure (RASP)**

One-way analysis of variance showed a significant difference in mean values of RASP among classes Ia, IIa and III (F = 40.99, df = 2 and 47, p < 0.001). There was a highly significant difference between patients in classes IIa and III (p < 0.001) but no significant difference between patients in classes IIa and Ia (fig. 1). The average age at the time of the established diagnosis did not differ significantly in classes IIa and III but did differ significantly in classes Ia and Ia (p < 0.01). All patients in class III had lower values than 40 mm Hg in RASP, independently of the presence of systemic hypertension and 68/69 patients in combined classes I and II had 40 mm Hg or higher RASP. In the latter two classes, patients with systemic hypertension usually had a high RASP (higher than 90 mm Hg).
There was a 20% or greater difference in retinal arterial systolic and/or diastolic pressure between both eyes, in only 2/8 patients with an unilateral normal common carotid system and the contralateral with 80% or greater stenosis. Of 30 patients with bilateral normal common carotid systems in this series, there were 3 with the above pressure differences between both eyes.

Cervical Arterial Stenoses and Retinal Vascular Changes

In all but one patient in class III there was evidence of microaneurysms (fig. 2) and/or arteriovenous anastomoses in the retinal vessels while in combined classes I and II these severe retinal vascular changes were not observed except in one patient with values lower than 40 mm Hg of RASP (table 1). There was no significant difference in incidence of dilatations of retinal small vessels between patients in classes Ia and IIa. In 79/81 patients, there was no significant difference in the severity of retinal vascular changes between both eyes.

Cervical Arterial Stenoses and Clinical Course

Age distribution, length of follow-up, occurrence of major severe events attributed to Takayasu’s disease, before and after the diagnosis, and major treatments except for symptomatic therapy in the 81 patients in classes I, II and III are presented in table 2. There were differences in the character of the events among the three classes. In class III, 6 patients (50%) experienced cerebral infarction and/or blindness during the period before or after the diagnosis, including 2 patients who died. These events did not occur in any patient in class II and in only 2 patients (3%) in class I. In class Ia, only one exceptional patient in whom the aortic arch vessels were most severely affected had lower values than 40 mm Hg in RASP and retinal microaneurysms. In this patient, intrapartum cerebral hemorrhage occurred after improvement in the retinal arterial pressure and the ocular fundi. During the follow-up period, 3 patients (25%) in class III obviously improved with an elevation of RASP to over 40 mm Hg, subsidence of syncopal attack and/or blurred vision and subsequent disappearance of arteriovenous anastomoses or microaneurysms in the retinal vessels. These subjective symptoms subsided in 5/6 patients in class II and the remaining one was asymptomatic through the period before and after the diagnosis until she died at age 70 with uterine cervix carcinoma.

The results at the time of the established diagnosis in 18 patients in classes III and II are summarized in table 3. In class I, and combined classes II and III, 15 patients (25%) of the 61 and 13 (72%) of the 18 belonged to the aortic arch type, and the remaining 46 (75%) and 5 (28%) to the extensive type, respectively. Incidence of the extensive type in combined classes II and III patients was significantly lower than that in class I patients ($p < 0.005$, chi-square method).

![FIGURE 2. Fluorescein fundus angiogram of the left eye in a 32-yr-old patient, case 11 in class III. Numerous microaneurysms composed of saccular or fusiform dilatations of precapillary arterioles and postcapillary venules.](http://stroke.ahajournals.org/)
TABLE 1  The Relationship of Cervical Arterial Stenoses to Retinal Arterial Systolic Pressure and to Retinal Vascular Changes in 50 Patients with Takayasu's Disease

| Classification according to severity of cervical arterial lesions | Age at diagnosis: mean ± SD (yr) | Total | Retinal arterial systolic pressure: lower than 40 mm Hg | Retinal vascular changes |
|---|---|---|---|---|---|
| Class III | 34.8 ± 9.9 | 12 | 12 (100%) | 11 (92%) | 1 (8%) | 0 |
| Class IIa | 41.2 ± 16.5 | 5 | 0 | 0 | 3 (60%) | 2 (40%) |
| Class Ia | 27.6 ± 7.7 | 33 | 1 (3%) | 1 (3%) | 11 (33%) | 21 (64%) |

Abbreviation: A-V = arteriovenous.

Discussion

A significant lowering of RASP and significant changes in retinal vessels did not occur before all of the 4CAS became markedly narrowed in patients with Takayasu's disease. Our results also demonstrated that once the RASP was lowered to less than 40 mm Hg, subsequent retinal microaneurysms and/or arteriovenous anastomoses usually appeared bilaterally and blindness and/or cerebral infarction often occurred.

In this series, patients who had the 3 cervical arterial systems with 70% or greater diameter stenosis or occlusion were divided into classes II and III, according to the degree of stenosis, with or without 50% or greater value in the remaining one system. This classification was useful in that a highly significant difference in RASP between classes IIa and III became apparent ($p < 0.001$, fig. 1). The data may assist in evaluating the 4 cervical arterial stenoses which relate to a significant lowering of RASP in Takayasu's disease. Eklof and Schwartz demonstrated that the overall cerebral blood flow remained unchanged in the baboon when the cervical stenosis of 91% constriction in the luminal area (equivalent to 70% in diameter) of the right common carotid artery was superimposed upon the preparation with the remaining three-vessel occlusion.

Of 6 patients in class II, 4 had occlusion of the 3 vessel systems and no narrowing of the remaining one, which was larger in diameter than the corresponding normal arterial system. In 2/4 patients, a selective arteriography in the artery without stenosis clearly revealed the six major cerebral arteries. Collateral vessels in the neck region were usually developed in patients in classes II and III, particularly in the former, and these findings were in accord with those of Sano et al. They and Lowe also found an adequate adaptation in the circle of Willis to occlusion of the carotid or vertebral arteries in this disease, and in the rabbit, respectively. In Takayasu's disease, these well-developed intra- and extracranial collateral circulations may prevent a reduction in retinal arterial pressure and the

TABLE 2  Clinical Course and Treatments in 81 Patients Classified by Angiographic Severity of Lesions of 4 Cervical Arterial Systems

<table>
<thead>
<tr>
<th>Clinical course and treatments</th>
<th>Class III (n = 12)</th>
<th>Class II (n = 6)</th>
<th>Class I (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to diagnosis</td>
<td>age at onset (mean ± SD)</td>
<td>25.4 ± 6.3 yr</td>
<td>23.2 ± 10.1 yr</td>
</tr>
<tr>
<td></td>
<td>age at diagnosis (mean ± SD)</td>
<td>34.8 ± 9.9 yr</td>
<td>39.7 ± 15.2 yr</td>
</tr>
<tr>
<td></td>
<td>cerebral infarction with sequelae</td>
<td>2 (17%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>cerebral hemorrhage or SAH</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>After diagnosis</td>
<td>length of follow-up (mean ± SD)</td>
<td>9.0 ± 5.1 yr</td>
<td>4.0 ± 2.7 yr</td>
</tr>
<tr>
<td></td>
<td>blindness (uni- or bilateral)</td>
<td>4 (33%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>cerebral infarction</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>cerebral hemorrhage or SAH</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>lethal heart failure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>deaths related to operation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>total number of patients who died of Takayasu's disease</td>
<td>2 (17%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>surgically treated patients</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>corticosteroid therapy</td>
<td>5 (42%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td></td>
<td>oral anticoagulant therapy</td>
<td>11 (92%)</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

Abbreviation: SAH = subarachnoid hemorrhage.
**TABLE 3 Clinical, Angiographic and Ophthalmological Results at the Time of Established Diagnosis in 18 Patients in Classes III and II**

<table>
<thead>
<tr>
<th>Case no</th>
<th>Onset Age (yr)</th>
<th>Diameter stenosis (%)</th>
<th>Common carotid Right</th>
<th>Vertebral Right</th>
<th>Retinal arterial pressure (mm Hg)</th>
<th>Retinal vascular changes, systemic complications attributed to the disease</th>
<th>Location of arterial lesions</th>
<th>ESR Westergren (mm/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III (3 ≥ 70%, 1 ≥ 50% stenosis): 12 patients</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>28</td>
<td>65</td>
<td>80</td>
<td>100</td>
<td>85</td>
<td>24/22</td>
<td>25/22</td>
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<tr>
<td>2*</td>
<td>28</td>
<td>46</td>
<td>100</td>
<td>100</td>
<td>65</td>
<td>100</td>
<td>10/8</td>
<td>10/8</td>
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<tr>
<td>3</td>
<td>14</td>
<td>16</td>
<td>70</td>
<td>100</td>
<td>100</td>
<td>75</td>
<td>27/22</td>
<td>21/14</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>35</td>
<td>100</td>
<td>80</td>
<td>50</td>
<td>75</td>
<td>Unmeasurable</td>
<td>28/18</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>23</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>70</td>
<td>26/22</td>
<td>21/17</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>39</td>
<td>85</td>
<td>95</td>
<td>100</td>
<td>100</td>
<td>34/34</td>
<td>31/24</td>
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<tr>
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<td>29</td>
<td>30</td>
<td>80</td>
<td>80</td>
<td>75</td>
<td>80</td>
<td>32/20</td>
<td>33/17</td>
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<tr>
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<td>30</td>
<td>33</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<td>18/10</td>
<td>25/10</td>
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<tr>
<td>9</td>
<td>33</td>
<td>48</td>
<td>100</td>
<td>95</td>
<td>55</td>
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<td>27/19</td>
<td>27/17</td>
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<tr>
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<td>47</td>
<td>50</td>
<td>75</td>
<td>80</td>
<td>100</td>
<td>30/16</td>
<td>24/14</td>
</tr>
<tr>
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<td>23</td>
<td>31</td>
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<td>80</td>
<td>100</td>
<td>100</td>
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<td>28</td>
<td>41</td>
<td>100</td>
<td>95</td>
<td>80</td>
<td>100</td>
<td>10/6</td>
<td>Unmeasurable</td>
</tr>
<tr>
<td>Class II (3 ≥ 70%, 1 &lt; 50% stenosis): 6 patients</td>
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<td></td>
<td></td>
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<td></td>
</tr>
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<td>13</td>
<td>38</td>
<td>63</td>
<td>100</td>
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<td>100</td>
<td>100</td>
<td>64/35</td>
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<td>53</td>
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<td>78/43</td>
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<td>37</td>
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<td>47/34</td>
<td>59/40</td>
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<tr>
<td>16</td>
<td>23</td>
<td>30</td>
<td>100</td>
<td>85</td>
<td>90</td>
<td>45</td>
<td>40/29</td>
<td>40/27</td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>23</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>47/30</td>
<td>44/30</td>
</tr>
<tr>
<td>18</td>
<td>14</td>
<td>32</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>95/43</td>
<td>108§/41</td>
</tr>
</tbody>
</table>

*Death.
†Because less than calibration.
‡Suppressed by corticosteroid therapy.
§Indicates pressure greater than calibration.
 Died with uterine cervix carcinoma.

Abbreviations: ESR = erythrocyte sedimentation rate; vas. = vascular; A-V = arteriovenous.

The appearance of microaneurysms in both eyes, if the lesions of the entire aortic arch vessels do not become severe and if there is no unfavorable variation in the circle of Willis.\(^19,20\) Such a potential compensatory adaptability in this disease may be attributed not only to the chronicity of the disease but also to the onset, at a young age. It seems that the bilaterality of the reduced retinal arterial pressure associated with the severe hypoxic retinopathy in this disease differs from a higher incidence of the unilaterality of the lowered retinal arterial pressure in a more aged patient with an acute stroke.\(^21\) This bilaterality is unlike the unilaterality of microaneurysms in a patient with ipsilateral atherosomatous obstruction of the internal carotid artery.\(^22\)

There have been many reports concerning the critical stenosis of a single vessel in humans\(^23-25\) and in laboratory animals,\(^26-28\) including the effects of the length of the critical stenosis.\(^25-28\) However, quantitative assessments of the integrated critical and pre-critical lesions of the affected 4CAS in combination with developed collateral vessels remain to be determined.

Concerning medical versus surgical treatment for the severely affected 4CAS in Takayasu's disease, there are no established data. In patients in class II, death has not been attributed to this disease and there were no severe complications during the follow-up period (table 2). In addition, there were no restrictions in daily life. Medical treatment consisted mainly of corticosteroid therapy for patients with the inflammatory active stage of the disease. One patient had a successful vaginal delivery after the diagnosis of Takayasu's disease had been made. Therefore, these patients in class II may be good candidates for medical treatment rather than reconstructive surgery of the affected aortic arch vessels, as are patients in class I.

In patients in class III, the prognosis for life span and/or the eyes was not always good, despite medical treatment. In one patient, retinal bleeding occurred...
after a bypass graft and a subsequent occlusion of the graft led to bilateral blindness. Although Kimoto reported successful operative results in 18 patients with severe or moderate lesions in the 4CAS in this disease, 3/18 operative deaths occurred and were attributed to intracerebral and subarachnoidal bleeding after the reconstruction of the aortic arch vessels. In one patient, retinal bleeding led to unilateral blindness. Kusaba et al. reported that one patient with this disease who had microaneurysms in both eyes died of massive frontal hemorrhage 5 days after the reconstruction of bilateral common carotid arteries. Thus, intracranial hemorrhage following cerebral arterial reconstruction occurs not only in patients with acute stroke but also in patients with severely affected aortic arch vessels in Takayasu’s disease, despite no evidence of fresh cerebral infarction. It may be difficult to determine whether a cerebral arterial reconstruction should be done for patients in class III, although surgery for cerebral ischemia is indicated in a limited number of cases.

In Takayasu’s disease, retinal arterial pressure and retinal vascular changes, particularly the former, responded well to the very severe occlusive lesions of all four cerebral arterial systems, independently of a development of collateral circulation in the neck region. These lesions do however, lead to a poor prognosis for life span and/or the eyes, regardless of the treatment. In this chronic disease, many patients have normal ocular fundi and a normal retinal arterial pressure, despite considerably severe lesions of the aortic arch vessels. Angiography is at present the most sensitive procedure to evaluate functional reserve capacity of the affected four vessels, including the developed collaterals, in transient ischemic attacks, carotid artery disease, and particularly in this gradually progressive disease in the younger generation.

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