

# **Multi-modal combination therapy rescued a frequent ischemic stroke patient due to giant cell arteritis**

Yoshiaki Takahashi, Kota Sato, Namiko Matsumoto, Yuko Kawahara, Taijun Yunoki, Jingwei Shang, Mami Takemoto, Nozomi Hishikawa, Yasuyuki Ohta, Toru Yamashita, and Koji Abe\*

Departments of Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan;

\*Corresponding to Professor Koji Abe, Department of Neurology, Okayama University Graduate School of Medicine and Dentistry, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.

Tel: +81-86-235-7365; Fax: +81-86-235-7368; E-mail: [deepblue.quality@gmail.com](mailto:deepblue.quality@gmail.com)

**Running head:** Frequent ischemic stroke with GCA

## **Abbreviations:**

CPA, cyclophosphamide; CT, computed tomography; DWI, diffusion-weighted image; EDV, end diastolic velocity; ESR, erythrocyte sedimentation rate; FAB, frontal assessment battery; <sup>18</sup>F-FDG, <sup>18</sup>F-fluoro-2-deoxy-2-d-glucose; GCA, giant cell arteritis; Gd, gadolinium; HE, hematoxylin-eosin; HIA, high intensity area; ICA, internal carotid artery; IMT, intima-media thickness; IS, ischemic stroke; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; PET, positron emission tomography; PSL, prednisolone; STA, superficial temporal artery; TIA, transient ischemic attack; WBC, white blood cell.

## **Abstract**

Ischemic stroke (IS) due to giant cell arteritis (GCA) is rare, but highly mortal. Here we report a 72-year-old man who showed frequent IS with GCA. Initial therapy with prednisolone increased the frequency of IS, which disappeared after continuous multi-modal combination therapy with corticosteroids, immunosuppressive agents, antiplatelets, and statin. The present case was discharged with independent walk, suggesting that a multi-modal combination therapy rescued the GCA patient from frequent IS.

**Key words:** combination therapy, contrast-enhanced magnetic resonance imaging, frequent ischemic stroke, Giant cell arteritis, temporal artery biopsy.

## **1 Introduction**

Cerebrovascular ischemic strokes (IS), which have been reported in 4 - 6 % of patients with giant cell arteritis (GCA), are the leading cause of mortality.<sup>1</sup> Here we report a case of frequent IS due to GCA which usually develops a serious course, but was rescued by multi-modal therapy with corticosteroids, immunosuppressive agents, antiplatelets, and statin.

## **2 Case report**

A man had been on medication for diabetes and hyperlipidemia from the age of 45. When he was 72 years old, he suddenly experienced dysarthria and right hemiparesis, which spontaneously disappeared 90 min after onset. Upon visiting our emergency clinic, he was admitted to our hospital. He showed a normal body temperature (36.1 °C) and no neurological deficits. Laboratory tests revealed a moderately elevated erythrocyte sedimentation rate (ESR, 38/71 mm). Brain magnetic resonance imaging (MRI) showed no high intensity area (HIA) with diffusion-weighted image (DWI, Fig. 1Aa). On the other hand, MR angiography (MRA) showed severe stenosis at the supraclinoid portion of the bilateral internal carotid arteries (ICAs, Fig. 1Ab, arrows). On day 4 of admission, he again presented transient right hemiparesis, when DWI showed HIA in the left frontal lobe (Fig.

1Ac, arrows), and was thus temporarily diagnosed with atherothrombotic stroke. He was discharged on day 28 after prescribing aspirin (100 mg) and pravastatin (5 mg).

However, he experienced transient aphasia and right upper limb paresis without any new lesions on DWI at 7 days after discharge, and was again admitted to our hospital. Based on recurrent IS with persistently high inflammatory responses, we suspected cervical/intracranial vasculitis. Gadolinium (Gd)-enhanced brain MRI showed intramural enhancement in both terminal ICAs (Fig. 1Ad, e, arrowheads) and in the superficial temporal artery (STA) (Fig. 1Af, g, arrowheads). T2 star-weighted image (T2\*WI) showed no intracranial microbleeds (not shown). Digital subtraction angiography (DSA) showed that the smoothly tapered vascular stenosis at the supraclinoid portions of ICA (Fig. 1B, arrow) without middle cerebral artery (MCA) stenosis, and the decreased blood flow velocity in distal part from the supraclinoid portions. A <sup>18</sup>F-fluoro-2-deoxy-2-d-glucose (<sup>18</sup>F-FDG) positron emission tomography (PET)/computed tomography (CT) scan showed increased uptake in bilateral common carotid arteries, the right subclavian artery, and the aortic arch (Fig. 1Ca-d, arrows). An STA biopsy on day 12 of the second admission showed significant intimal thickening (Fig. 1Da, arrows), epithelioid granuloma (Fig. 1Db, arrows), and giant cell formation (Fig. 1Dc, arrows).

The patient was thus diagnosed with recurrent IS due to GCA, and was treated with prednisolone (PSL, 60 mg) and cyclophosphamide (CPA, 500 mg). Although ESR

decreased immediately to a normal range after this combination therapy, carotid artery ultrasound showed a gradual increase of intima-media thickness (IMT) and a reduction in end diastolic velocity (EDV) of the ICA (Fig. 1E, upper columns). He developed at least 10 TIAs and four strokes (Fig. 1E, middle column) within 4 weeks, and his gait disturbance and frontal lobe function gradually worsened (frontal assessment battery (FAB); from 17/18 on the second admission to 5/18 on day 35). However, such frequent ischemic attacks disappeared soon after replacing pravastatin (5 mg) with atorvastatin (10 mg) on day 47 followed by antiplatelet oral cilostazol (50 – 100 mg) and ozagrel infusion (80 mg) from day 53, and methotrexate (6 mg/week) from day 66. On day 108, he was discharged, walked independently, and FAB recovered to 17/18.

### **3 Discussion**

The present case showed frequent IS with intracranial artery stenosis due to GCA, but was successfully rescued by combination therapy of steroids, immunosuppressants, antiplatelets, and statin. Although the present case had not showed typical clinical symptoms of GCA such as headache, jaw claudication, and enlarged temporal artery, these symptoms' sensitivities were low.<sup>2</sup> The positive temporal artery biopsy and the findings of inflammatory in the large arteries on MRI and <sup>18</sup>F-FDG PET/CT scan were also important

findings for meeting the criteria of GCA as well as specific clinical symptoms.<sup>3</sup> Thus, he was diagnosed with GCA.

MRA of the present case depicted poorer MCA related with worsened his symptoms. On the other hand, DSA showed the severe stenosis at the supraclinoid portions of ICA without MCA stenosis (Fig. 1B, arrow). Decreased arterial signal on MCA might be caused by the hypoperfusion of MCA due to ICA stenosis. Furthermore, the reversible arterial wall thickening after treatment on enhanced MRI suggested vasculitis (Fig. 1E, lower column). Although cerebral infarction at corona radiata was atypical for GCA, the previous report showed that partial internal watershed infarction was associated with hemodynamic impairment with ICA steno-occlusion.<sup>4</sup> These results suggested that the main pathological mechanism of the present case was hemodynamic etiology caused by bilateral ICA stenosis due to GCA.

High-dose glucocorticoid therapy is well established for the treatment of IS due to GCA, and antiplatelet and statin therapy may also be effective.<sup>5, 6</sup> However, in the present case, IS frequency increased and both IMT and EDV worsened (Fig. 1E), even after steroid therapy. Steroid therapy might not rapidly improve the organized intima thickening, may even activate platelet thromboxane, and promotes vascular occlusion.<sup>7</sup> On the other hand, a combination of corticosteroids plus immunosuppressive agents or antiplatelet therapy appears to be beneficial in patients with IS due to GCA.<sup>1, 5</sup> Furthermore,

cilostazol shows not only an antiplatelet but also a vasodilatory effect by inhibiting phosphodiesterase 3, subsequently raising the level of intracellular cAMP.<sup>8</sup> In fact, the present case showed a gradual improvement of IMT and EDV ultrasound findings as well as improved symptoms after continuous multi-modal therapy including additional cilostazol therapy (50 – 100 mg) (Fig. 1E). Although the second administration of cyclophosphamide might be effective, the first administration of cyclophosphamide was not effective. Therefore, we considered that the vasodilatory effect of cilostazol was clinically more effective.

IS due to GCA is rare and shows a mortality rate as high as 53%.<sup>1</sup> However, the present case suggests that multi-modal combination therapy was able to rescue GCA patient with frequent IS with ITAs and lacunes.

## **Acknowledgement**

We appreciate the cooperation of the patients. This work was partly supported by a Grant-in-Aid for Scientific Research (B) 17H0419619, (C) 15K0931607, 17H0419619 and 17K1082709, and by Grants-in-Aid from the Research Committees (Kaji R, Toda K, and Tsuji S) from Japan Agency for Medical Research and Development (AMED). The authors declare no conflicts of interest.

## References

1. Alsolaimani RS, Bhavsar SV, Khalidi NA et al. Severe Intracranial Involvement in Giant Cell Arteritis: 5 Cases and Literature Review. *The Journal of Rheumatology*. 2016; **43**: 648-56.
2. Smetana GW, Shmerling RH. Does this patient have temporal arteritis?. *JAMA*. 2002; **287**: 92-101.
3. Hunder GG, Bloch DA, Michel BA et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum*. 1990; **33**: 1122-8.
4. Li Y, Li M, Zhang X et al. Clinical features and the degree of cerebrovascular stenosis in different types and subtypes of cerebral watershed infarction. *BMC Neurol*. 2017; **17**: 166.
5. Martinez-Taboada VM, Lopez-Hoyos M, Narvaez J, Munoz-Cacho P. Effect of antiplatelet/anticoagulant therapy on severe ischemic complications in patients with giant cell arteritis: a cumulative meta-analysis. *Autoimmunity Reviews*. 2014; **13**: 788-94.
6. Pugno G, Sailler L, Bourrel R, Montastruc JL, Lapeyre-Mestre M. Is statin exposure associated with occurrence or better outcome in giant cell arteritis? Results from a French population-based study. *The Journal of Rheumatology*. 2015; **42**: 316-22.

7. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. *Medicine*. 2009; **88**: 227-35.
8. Zhou Q, Liao JK. Pleiotropic effects of statins. - Basic research and clinical perspectives. *Circulation journal*. 2010; **74**: 818-26.

## Figure legend

Fig. 1) (A) MRI and MRA on day 1 (a, b) of first admission, showing no HIA on DWI (a), severe stenosis in the supraclinoid portion of the bilateral ICAs (b, arrows). DWI on day 4 of the first admission showed HIAs in the left corona radiata (c, arrows). Axial (d, f, g) and sagittal (e) gadolinium-enhanced T1-weighted vessel wall MRI on day 5 of the second admission, showing intramural enhancement and thickening in both terminal ICAs (d, e, arrowheads) and STA (f, g, arrowheads). (B) DSA showed the smoothly tapered vascular stenosis at the supraclinoid portions of ICA (arrow), but without MCA stenosis. (C)  $^{18}\text{F}$ -FDG PET/CT scan, showing increased uptake in bilateral CCAs (a, b, arrows), the right subclavian artery (a, c, arrowheads), and the aortic arch (a, d, open arrowheads). (D) HE staining of right STA, showing significant intimal thickening (a, arrows), epithelioid granuloma (b, arrows), and giant cell formation (c, arrows). Scale bars: a-c = 200  $\mu\text{m}$ . (E) Hospital course (ESR, carotid artery ultrasound, NIHSS, MRI and MRA) and medication of the patient during second admission.