

Two cases of IgG4-related disease accompanied by many cerebral microbleeds and a review of the literature: can IgG4-related disease cause cerebral small vessel vasculitis/vasculopathy?

Katsuyuki Ukai^{1,2}

¹*Department of Psychogeriatrics, Kamiida Daiichi General Hospital, Nagoya, Japan*
²*Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan*

ABSTRACT

IgG4-related disease (IgG4-RD) is a condition of unknown cause, which involves marked tissue infiltration by IgG4-positive plasma cells into various organs throughout the body. Histopathological examinations based on biopsy examinations are essential for obtaining a definitive clinical diagnosis of IgG4-RD. However, there are only a limited number of organs from which biopsy samples can be easily obtained. Furthermore, it is impossible even for recently developed imaging techniques to directly detect abnormalities affecting small organs, such as the cerebral small vessel system. Due to these limitations, the clinical diagnosis of so-called “IgG4-related cerebral small vessel vasculitis/vasculopathy” is very difficult. In this report, two cases of IgG4-RD involving elderly patients are presented, together with their cranial magnetic resonance imaging features, especially those seen on T2* imaging. Both patients exhibited many cerebral microbleeds (CMB) on T2* imaging. I consider that it is possible to indirectly detect abnormalities of the small cerebral vessels by searching for CMB because they are caused by the failure of small cerebral vessels. Of course, the fact that many CMB were seen in both cases might be considered to be a coincidence. However, the chances of this are low because a rapid increase in the number of CMB, as was seen in case 1, and the occurrence of so many CMB, as was seen in case 2, are rare. Based on my clinical experiences and the detailed findings of the IgG4-RD cases described in this report, I present the hypothesis that “IgG4-related cerebral small vessel vasculitis/vasculopathy” exists.

Keywords: cerebral microbleeds, cerebral small vessel vasculitis, IgG4-related disease, T2* imaging, treatable dementia

Abbreviations:

CAA: cerebral amyloid angiopathy
CMB: cerebral microbleeds
CT: computed tomography
FLAIR: fluid-attenuated inversion recovery
IgG4-RD: IgG4-related disease
MMSE: Mini-Mental State Examination
MRI: magnetic resonance imaging

Received: October 7, 2020; accepted: December 25, 2020

Corresponding Author: Katsuyuki Ukai, MD, PhD

Department of Psychogeriatrics, Kamiida Daiichi General Hospital, 2-70 Kamiida-Kitamachi, Kita-ku, Nagoya 462-0802, Japan

Tel: +81-52-991-3111, Fax: +81-52-981-6879, E-mail: ukai777@kamiida-hp.jp

This is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

INTRODUCTION

IgG4-related disease (IgG4-RD) is a condition of unknown cause, which involves marked tissue infiltration by IgG4-positive plasma cells in various organs throughout the body. The pancreas/bile ducts and lacrimal/salivary glands are the most frequently affected tissues/organs; however, other tissues/organs, such as the kidneys, lungs, retroperitoneum, heart, aorta, pituitary gland, dura mater, and peripheral nerves, can also be affected.¹⁻⁶ Steroid therapy is almost always effective against IgG4-RD, but the relapse rate of IgG4-RD after the discontinuation of steroid therapy is high. The role of IgG4 in the pathogenesis of IgG4-RD is unclear.

The following comprehensive diagnostic criteria for IgG4-RD were established by a Japanese research team in 2011: 1) an elevated serum IgG4 level (>135 mg/dl); 2) swelling, mass formation, nodule formation, and/or thickening of tissues/organs; 3) characteristic histopathological findings, including during immunostaining; and 4) the exclusion of similar diseases.^{1,2} Thus, histopathological examinations based on either autopsy or biopsy examinations are essential for the definitive diagnosis of IgG4-RD. However, in clinical practice there are only a limited number of organs from which biopsy samples can be easily obtained. Furthermore, some symptoms, such as organ swelling, can be detected via imaging examinations when large organs are affected, but in cases involving small organs/tissues, such as the cerebral small vessel system, it is impossible even for recently developed imaging techniques to detect such abnormalities. Due to these limitations, the diagnosis of so-called “IgG4-related cerebral small vessel vasculitis/vasculopathy” is difficult, unless it is specifically searched for at autopsy. Therefore, there are few reports about this condition in the literature, and its effects on cognitive functions are unknown.

In this report, two cases of IgG4-RD that were treated at my outpatient clinic are presented, together with their cranial magnetic resonance imaging (MRI) features, especially those seen on fluid-attenuated inversion recovery (FLAIR) and T2* imaging. In addition, the possible pathology of the disease is discussed.

CASE REPORT

Informed consent for the publication of this report was obtained from the patients and their families. Minor modifications to the case details, which did not interfere with important data, were made to preserve the patients' anonymity.

Case 1

In August of 200X-1, a male in his early 70s was admitted to the Department of Gastroenterology of my hospital with severe appetite loss. Abdominal computed tomography (CT) and magnetic resonance cholangiopancreatography revealed a swollen pancreas, stenosis of the common bile duct, and right-sided hydronephrosis (Figure 1). His serum IgG4 level was high (358 mg/dl). Since a biopsy could not be performed, he was diagnosed with possible IgG4-related pancreatitis and probable IgG4-related sclerosing cholangitis by gastroenterologists.¹⁻³ Steroid therapy, involving 30 mg/day prednisolone, was administered, and his condition improved markedly, as did his abdominal CT findings. In November 200X-1, he visited the Department of Neurology complaining of forgetfulness. Cranial MRI was performed. FLAIR imaging showed mild high-intensity lesions in the periventricular white matter, and T2* imaging revealed many

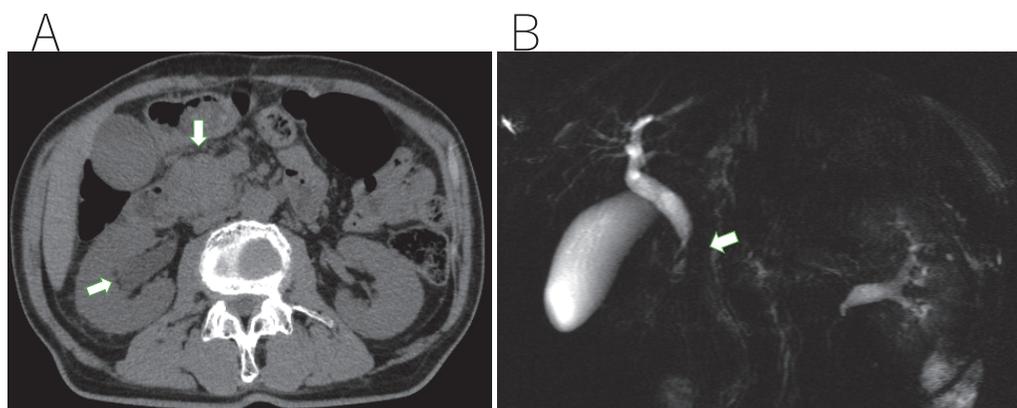


Fig. 1 Abdominal computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) findings of case 1

Fig. 1A: Abdominal CT showed a swollen pancreas and right-sided hydronephrosis (white arrows).

Fig. 1B: MRCP revealed that the common bile duct had become stenotic (white arrow).

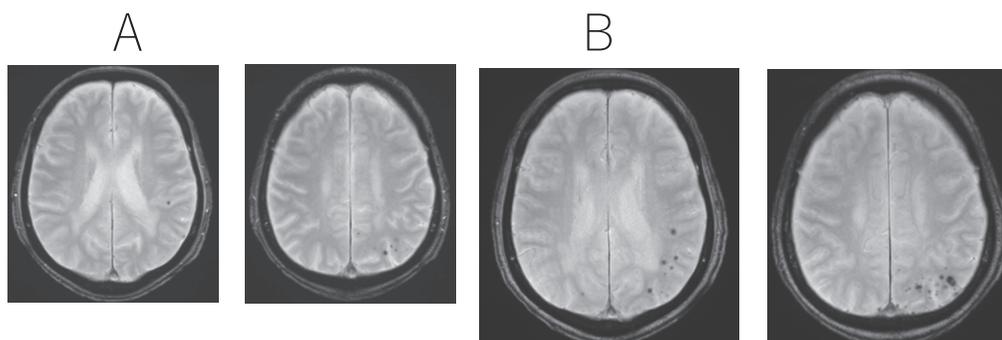


Fig. 2 Cranial magnetic resonance imaging (MRI) findings of case 1

Fig. 2A: The first cranial MRI scan performed in 200X-1 revealed many cerebral microbleeds (CMB), mainly in the left occipital lobe on T2* imaging.

Fig. 2B: The third cranial MRI scan performed in 200X+1 showed that the number of CMB had increased and that CMB were now present in the left occipital and parietal lobes, as well as the right occipital lobe.

cerebral microbleeds (CMB), mainly in the left occipital lobe (Figure 2A).

In June of 200X, he attended my clinic, complaining of forgetfulness and irritability, together with his wife. He was receiving 10 mg/day of prednisolone. His Mini-Mental State Examination (MMSE) score was 27 points (attention: -3), and T2* imaging performed during a second cranial MRI scan revealed that the number of CMB had increased from 30 to 80 (visual estimate), although no changes in the high-intensity areas of the periventricular white matter were seen on FLAIR imaging. Since the patient did not show any recent memory impairment, it was considered that there was a strong possibility that he was suffering from a symptomatic cognitive disorder and/or a vascular neurocognitive disorder rather than a more common form of dementia, such as Alzheimer's disease. Thus, he was followed up without any anti-dementia drugs being administered.

A third cranial MRI scan performed in 200X+1 showed that the number of CMB had further

increased to 110 (visual estimate) and that CMB were now present in the left occipital and parietal lobes, as well as the right occipital lobe, although no changes were seen on FLAIR imaging (Figure 2B). The patient's MMSE was 26 (attention: -4). At that time, he was receiving 15 mg/day of prednisolone.

In 200X+2, he was still receiving steroid therapy (at the same dose), his condition was favorable, and his MMSE had improved to 30.

Case 2

In 200X-5, a male in his early 70s was admitted to my hospital with a fever of unknown cause. He consulted the Department of Ophthalmology and was definitively diagnosed with IgG4-related ophthalmic disease by ophthalmologists based on his high serum IgG4 level and CT and biopsy findings.⁴ Steroid therapy was administered, and his condition improved.

In 200X, he visited my clinic with a chief complaint of forgetfulness. The steroid therapy had already been discontinued. His serum IgG4 level remained high (1590 mg/dl). His MMSE score was 17, and T2* imaging performed during cranial MRI revealed innumerable CMB throughout his brain, although FLAIR imaging only showed mild high-intensity lesions in the periventricular white matter (Figure 3). A diagnosis of a strong possibility of symptomatic and/or vascular dementia was made, and the patient was followed up without any anti-dementia drugs being administered. Instead, non-drug therapies, such as physical and mental exercises, were introduced.

In 200X+1, his MMSE score recovered to 24 points (orientation: -3, attention: -3).

In 200X+5, cranial MRI was performed and did not show any marked changes. FLAIR imaging did not show any changes at all, and it was difficult to visually determine whether the number of CMB had increased/decreased on T2* imaging because there were countless CMB.

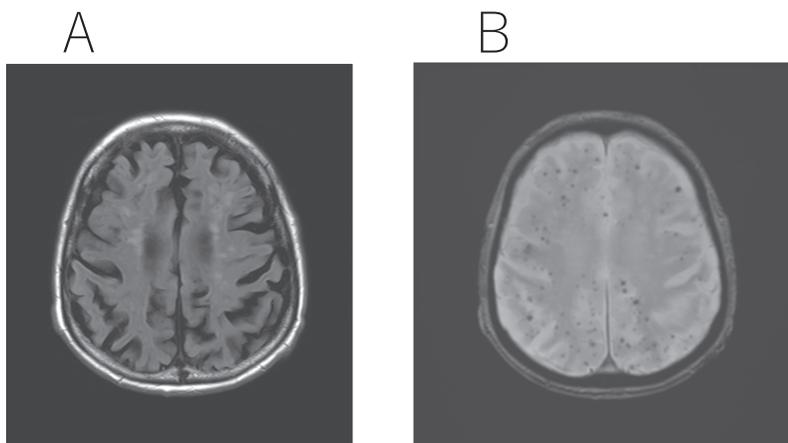


Fig. 3 Cranial MRI findings of case 2

Fig. 3A: FLAIR imaging showed mild high-intensity lesions in the periventricular white matter.

Fig. 3B: T2* imaging revealed numerous CMB throughout the brain, which were distributed independently of the white matter lesions.

DISCUSSION

Does “IgG4-related cerebral small vessel vasculitis/vasculopathy” exist?

Assuming that “IgG4-related cerebral small vessel vasculitis/vasculopathy” exists, are the abnormalities it causes only detectable at autopsy? As mentioned above, it is impossible to detect them directly, but I consider that it is possible to indirectly detect them by searching for CMB on T2* imaging because CMB are caused by the failure of small cerebral blood vessels, especially capillaries.

CMB are known to be caused by several diseases. The most representative types of CMB are hypertensive CMB (deep type) and cerebral amyloid angiopathy (CAA)-related CMB (lobar type). Other pathologies that might cause CMB are considered to include (1) primary central nervous system small vasculitis, (2) hereditary cerebral vasculopathy (e.g., CADASIL, CARASIL, and CARASAL), (3) autoimmune cerebral vasculopathy (e.g., ANCA-related vasculitis syndrome, autoimmune complex angiopathy, and collagen diseases), and (4) hereditary leukoencephalopathy (e.g., Alexander’s disease). However, it remains unclear to what extent these diseases can cause CMB.

The two cases of IgG4-RD presented above are the only cases of IgG4-RD experienced by my department. Of course, the fact that a lot of CMB were seen in both cases of IgG4-RD might be considered to be a coincidence. However, I suggest that this might not be a coincidence for the following reasons: (1) Based on my clinical experience, the chances of this being a coincidence are low because even in typical cases of Alzheimer’s disease a rapid increase in the number of CMB, as was seen in case 1, and the occurrence of so many CMB, as was seen in case 2, are rare. (2) When CAA-related inflammation is induced, it is common for the distribution of CMB to be consistent with that of marked white matter lesions. However, in the two cases described above it was considered that CAA-related inflammation did not occur because in both cases the white matter lesions that arose were mild, stable, and only affected the periventricular regions (these lesions were thought to be related to ischemic changes), and most of the CMB were located away from the white matter lesions and increased in number independently of the white matter lesions. Therefore, it is unlikely that CAA caused the frequent occurrence of CMB seen in these cases. (3) A previous study, in which sural nerve biopsy specimens were examined, suggested that a close relationship exists between IgG4-related pathology and small vessel vasculitis.⁷ Based on these factors, I hypothesize that “IgG4-related cerebral small vessel vasculitis/vasculopathy/capillary disorder” exists.

Previous studies describing CMB being detected on cranial MRI in IgG4-related disease

To the best of my knowledge, there has only been one case report involving a description of CMB associated with IgG4-RD in the literature.⁸ In that case, as in the present cases, no brain biopsy was performed; however, the patient was diagnosed with possible IgG4-related cerebral vasculitis/leptomeningitis, although it was also mentioned that CAA could not be completely ruled out. The white matter lesions in that case disappeared after steroid therapy. Other similar IgG4-RD cases in which brain parenchymal lesions disappeared after steroid therapy have been reported.⁹

Unlike in the latter case,⁸ the CMB in the present cases were distributed separately from and increased in number independently of the white matter lesions. Why was this? Conversely, why did the white matter lesions remain stable despite the increase in the number of CMB? I consider that the white matter lesions seen in the present cases were related to ischemic changes, which are usually observed in elderly people. Furthermore, I suggest that in addition to brain parenchymal lesions IgG4-RD might also cause CMB, as was seen in the present cases, although

the pathology of such brain parenchymal lesions remains unclear.

This is only the second case report involving descriptions of CMB associated with IgG4-RD in the literature. It is expected that further studies based on the accumulation of IgG4-RD cases and the use of cranial MRI would help to elucidate the relationship between IgG4-RD and CMB. Furthermore, although IgG4-RD might sometimes cause cognitive impairment, steroid therapy is generally effective against IgG4-RD-induced inflammation. Thus, there is a possibility that IgG4-RD might be a form of so-called “treatable dementia”.^{8,9} I consider that psychiatrists should pay more attention to this disease.

ACKNOWLEDGEMENT

I am grateful to Prof. Tetsuro Nagasaka of the Department of Pathology, Nagoya University Graduate School of Medicine, for his cooperation. No grants or other sources of funding were received for this study.

DISCLOSURES

The author has no potential conflicts of interest to disclose. The author received speaker’s honoraria from Eisai in 2019.

REFERENCES

- 1 Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol*. 2012;22(1):1–14. doi:10.1007/s10165-011-0508-6.
- 2 Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4- related disease (IgG4-RD), 2011. *Mod Rheumatol*. 2012;22(1):21–30. doi:10.1007/s10165-011-0571-z.
- 3 Ohara H, Okazaki K, Tsubouchi H, et al. Clinical diagnostic criteria of IgG4- related sclerosing cholangitis 2012. *J Hepatobiliary Pancreat Sci*. 2012;19(5):536–542. doi:10.1007/s00534-012-0521-y.
- 4 Goto H, Takahira M, Azumi A, Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. *Jpn J Ophthalmol*. 2015;59(1):1–7. doi:10.1007/s10384-014-0352-2.
- 5 Chan SK, Cheuk W, Chan KT, Chan JKC. IgG4- related sclerosing pachymeningitis: A previously unrecognized form of central nervous system involvement in IgG4-related sclerosing disease. *Am J Surg Pathol*. 2009;33(8):1249–1252. doi:10.1097/PAS.0bo13e3181abdfc2.
- 6 Ohyama K, Koike H, Iijima M, et al. IgG4-Related Neuropathy. *JAMA Neurol*. 2013;70(4):502–505. doi:10.1001/jamaneurol.2013.658.
- 7 Ohyama K, Koike H, Takahashi M, et al. Immunoglobulin G4-related pathologic features in inflammatory neuropathies. *Neurology*. 2015;85(16):1400–1407. doi:10.1212/WNL.0000000000002039.
- 8 Usami T, Kawashima S, Ueki Y, Toyoda T, Okita K, Matsukawa N. Early treatment for IgG4-related disease may prevent cognitive impairment caused by cerebral vasculitis: A case report and review of the literature. *eNeurologicalSci*. 2018;10:45–47. doi:10.1016/j.ensci.2017.12.005.
- 9 Temmoku J, Sato S, Matsumoto H, et al. IgG4-related disease complicated by brain parenchymal lesions successfully treated with corticosteroid therapy: A case report. *Tohoku J Exp Med*. 2020;251(3):161–168. doi:10.1620/tjem.251.161.