analysis of variance (Wilcoxon/Kruskal-Wallis test, chi-square approximation). Comparisons of visual field improvement and visual acuity improvement in MOG-Ab–positive and –negative cases were analysed using chi-square test followed by Fisher exact test.

RESULTS

Disease Type

The disease types of all (70) patients were CRION in 2 patients, AQP4-Ab seropositive optic neuritis (neuromyelitis optica) in 13, idiopathic optic neuritis in 34, and optic neuritis associated with multiple sclerosis in 21.

Eighteen of 70 patients (25.7%) were positive for MOG-Abs. The 18 patients comprised 7 males and 11 females. The disease types of 18 MOG-Ab seropositive patients were CRION in 2 patients, AQP4-Ab seropositive optic neuritis (neuromyelitis optica) in 2, idiopathic optic neuritis in 12, and optic neuritis associated with multiple sclerosis in 2. The disease types and patient background are shown in Table 1. Eight patients had bilateral optic neuritis (Nos. 1, 3, 4, 5, 11, 13, 16, and 17). In patients with bilateral optic neuritis, we selected the more severe eye for evaluation in the present study. Accordingly, the left eye was studied in Nos. 1, 3, 4, 5, 13, 16, and 17, and the right eye in No. 11 (Table 2).

Number of Relapses

The numbers of relapses in all the MOG-Ab seropositive patients were investigated. Case 4 experienced 8 relapses, which was the largest number of all patients. The mean number of relapses per year was 0.40 in MOG-Ab seronegative patients and 0.82 in seropositive patients, and was significantly greater in MOG-Ab seropositive than in seronegative patients (Figure 1).

TABLE 1 Disease types of MOG-Ab seropositive cases.

Disease type	No. of MOG-Ab seropositive cases/No. of all cases
Chronic relapsing inflammatory optic neuropathy (CRION)	2/2
Neuromyelitis optica (NMO)	2/13
Idiopathic optic neuritis	12/34
Multiple sclerosis (MS) with optic neuritis	2/21

Visual Outcome

Visual acuity and visual field deficit before and after treatment in MOG-Ab seropositive patients were analysed. In case 1 (CRION), visual acuity at disease onset was light perception negative. Subsequently, this case had 4 relapses. Although steroid pulse therapy improved visual acuity to 20/13, visual field deficit of enlarged Mariotte blind spot remained. All patients, excluding cases 4 and 9, had visual acuity improvement of two lines or more, but some kind of visual field deficit remained in all patients. The visual field at the time of acute exacerbation of optic neuritis showed diverse patterns, including central scotoma, paracentral scotoma, temporal field cut, and complete visual field cut.

The relation between MOG-Ab status and visual acuity improvement was analysed. In MOG-Ab seropositive patients, visual acuity did not improve in only 2 patients, 1 with AQP4-Ab optic neuritis and 1 with idiopathic optic neuritis, whereas visual acuity was improved in 16 of 18 patients (88.9%). In MOG-Ab seronegative patients, visual acuity was improved in 37 of 52 patients (71.2%) and was not significantly difference from the seropositive group.

Next, the relation between MOG-Ab status and visual field improvement was analysed. Visual field deficit remained after treatment in 14 of 18 (77.8%) MOG-Ab seropositive patients. In MOG-Ab seronegative patients, visual field deficit remained after treatment in 16 of 52 patients (30.8%). Comparing these figures, residual visual field defect was significantly more common in MOG-Ab seropositive patients ($p = 0.0015$).

Representative Cases

Figures 2 and 3 show the results of visual field measurements in a representative case (No. 17). A 33-year-old man with multiple sclerosis presented at our hospital because of decreased visual acuity and visual field abnormality in both eyes. Examination showed mild reddening of the optic disc in both eyes. Visual field examination showed central scotoma and nasal scotoma in the right eye and temporal scotoma in the left eye (Figure 2). Corrected visual acuity was 20/25 in the right eye and 20/66 in the left eye. MRI revealed hyperintensity in bilateral optic nerves. Optic neuritis associated with multiple sclerosis was diagnosed. In the cell-based assay for MOG-Abs, this case gave the strongest antigen-antibody reaction among the MOG-Ab seropositive cases. After steroid pulse therapy, corrected visual acuity improved to 20/22 in the right eye and 20/33 in the left eye. Thereafter the patient had 4 relapses. At each relapse, steroid pulse therapy preserved visual acuity, but Goldmann

TABLE 2 Summary of individual MOG-Ab seropositive cases.

Case no.	Age	Gender	Disease	Vision improvement	Relapse	Visual field deficit	Ocular pain	Bilateral/ unilateral
1	26	F	CRION	+	4	+	–	B
2	30	M	CRION	+	4	+	–	U(R)
3	41	F	NMO	+	4	+	–	B
4	48	F	NMO	–	8	+	–	B
5	28	F	Idiopathic optic neuritis	+	2	+	–	B
6	39	F	Idiopathic optic neuritis	+	1	+	–	U(R)
7	52	F	Idiopathic optic neuritis	+	2	+	–	U(L)
8	42	F	Idiopathic optic neuritis	+	2	+	–	U(L)
9	64	F	Idiopathic optic neuritis	–	2	+	–	U(R)
10	50	F	Idiopathic optic neuritis	+	1	–	–	U(L)
11	51	M	Idiopathic optic neuritis	+	2	–	+	B
12	30	F	Idiopathic optic neuritis	+	1	–	+	U(R)
13	43	M	Idiopathic optic neuritis	+	1	–	+	B
14	18	F	Idiopathic optic neuritis	+	1	+	–	U(L)
15	52	M	Idiopathic optic neuritis	+	1	+	+	U(R)
16	51	M	Idiopathic optic neuritis	+	2	+	–	B
17	33	M	MS with optic neuritis	+	4	+	–	B
18	48	M	MS with optic neuritis	+	1	+	+	U(L)

CRION = chronic relapsing inflammatory optic neuropathy; NMO = neuromyelitis optica; MS = multiple sclerosis; B = bilateral; U = unilateral; R = right; L = left.

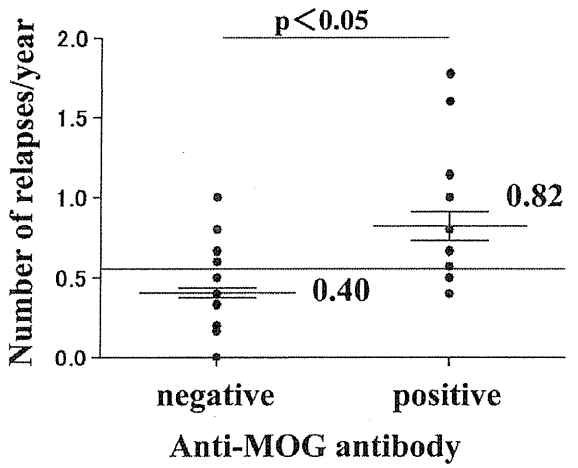

FIGURE 1 Analysis of the number of relapses per year. The number of relapses per year was significantly greater in MOG-Ab seropositive cases than in seronegative cases ($p<0.05$ by Wilcoxon/Kruskal-Wallis test, chi-square approximation).

visual field test showed residual central scotoma in the right eye and temporal field cut in the left eye (Figure 3).

Figure 4 shows the visual field findings of the case (No. 4) that had the largest number of relapses. A 48-year-old woman had AQP4-Ab seropositive optic neuritis (neuromyelitis optica). Corrected visual acuity at onset was 20/500. She was treated with steroid pulse therapy and plasmapheresis, but subsequently had a total of 8 relapses (seven times in the left eye, once in the right eye). Visual field test at the last follow-up showed residual visual field in only a part of the inferior field (Figure 4), with corrected visual acuity of 20/2000 in the left eye.

DISCUSSION

A recent study has recommended measurement of MOG-Abs in patients with neuromyelitis optica negative for anti-AQP4 antibodies considered to be specific for neuromyelitis optica.[13] In the present study, MOG-Abs were positive in 18 of 70 patients with optic neuritis. The disease types found in MOG-Ab seropositive optic neuritis included CRION, neuromyelitis optica, idiopathic optic neuritis, and multiple sclerosis. Among them, idiopathic optic neuritis was the prominent type. Other report has also indicated that patients with MOG-Ab–positive neuromyelitis optica or neuromyelitis optica spectrum disorder tend to relapse.[14] On the other hand, MOG-Abs are also found in multiple sclerosis patients, although the titres are low. In our series, MOG-Abs were positive in two cases of optic neuritis associated with multiple sclerosis. The disease with the largest number of MOG-Ab–positive cases was idiopathic optic neuritis. We also observed that MOG-Abs were not detected in anterior ischaemic optic neuropathy, suggesting a weak association of MOG-Abs with non-inflammatory ocular disease (data not shown). In addition, high MOG-Ab titres have been reported to be prominently detected in patients with recurrent optic neuritis.[7] Case 17 in our series was strongly positive for MOG-Abs, and this case had 4 relapses with residual visual field deficit. Furthermore, in our previous report, cases double positive for MOG-Abs and AQP4-Abs were particularly refractory to treatment, progressed rapidly, and tended to become resistant to treatment.[6] Case 4 in the present series was positive for both MOG-Abs and AQP4-Abs. In this case, despite courses of treatments, optic neuritis

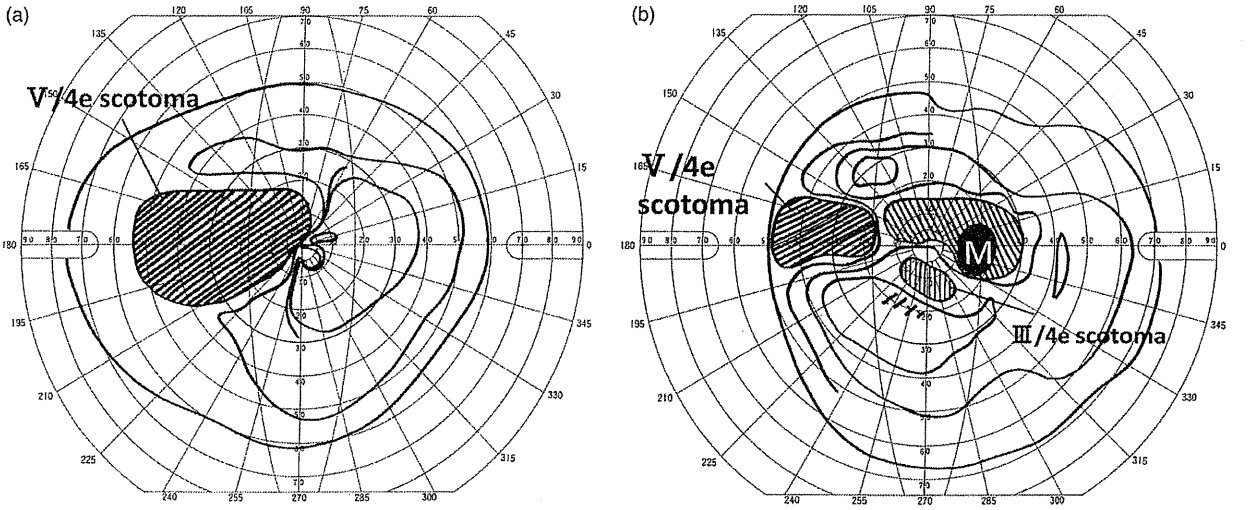

FIGURE 2 Case 17: Goldmann visual field in left eye (a) and right eye (b) at initial onset. Pre-treatment visual field test showed scotoma from the centre to temporal side in the left eye (a), and central scotoma and nasal scotoma in the right eye (b). Corrected visual acuity was 20/66 in the left eye and 20/25 in the right eye.

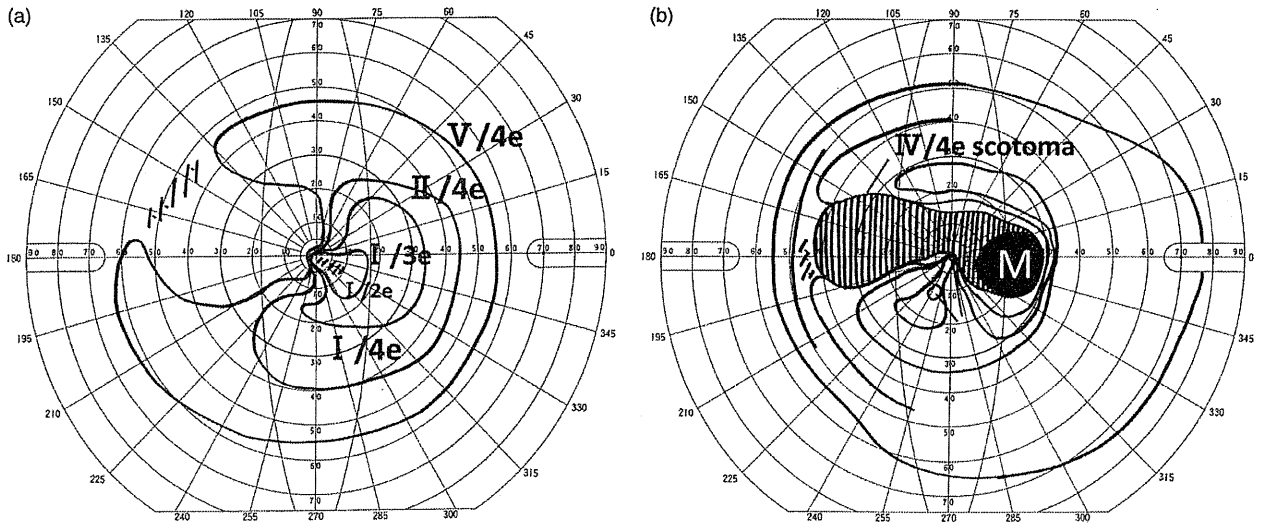

FIGURE 3 Case 17: Goldmann visual field of the left eye (a) and right eye (b) at the last follow-up. After the initial onset, the lesion recurred four times, and was treated with steroid pulse therapy every time. Visual field test at the last follow-up showed temporal field cut remaining in the left eye (a), and central scotoma remaining in the right eye (b). Corrected visual acuity was 20/22 in the right eye and 20/33 in the left eye, with improvement of 2 lines or more, which has been maintained until the present.

recurred repeatedly with residual visual field deficit resulting in no improvement in visual acuity.

MOG-Abs are a marker of demyelination in the central nervous system and not an indicator of astrocyte damage.[11,15] MOG-Ab seropositive optic neuritis probably involves demyelination between the optic nerve and optic tract, which responds well to a sequence of early treatment resulting in improvement of central visual field but leaving residual peripheral visual field deficits. If regeneration of the damaged myelin sheath occurs, nervous function would recover with improvement of symptoms. However, when demyelination occurs repeatedly, delay in treatment may lead to axonal damage, and improvement in symptoms cannot be expected. In our series also, a significant number of cases had some kinds of residual visual field deficit.

The clinical characteristics of MOG-Ab seropositive optic neuritis include widespread involvement of the optic nerve and damages extending from the optic chiasma to the optic tract, which are similar to those of AQP4-Ab seropositive optic neuritis. Clinically, this

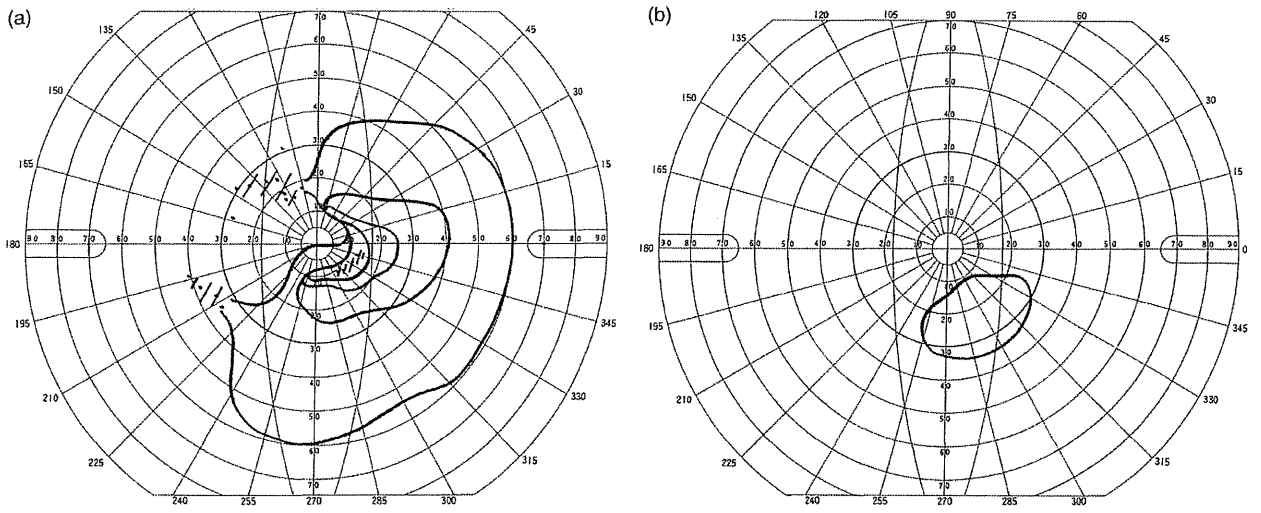

FIGURE 4 Case 4: Goldmann visual field of the left eye at initial onset (a) and at the last follow-up (b). After the initial onset, the patient had 8 subsequent relapses. At onset, widespread temporal field cut was observed (a), and corrected visual acuity was 20/500. Steroid pulse therapy and plasmapheresis were conducted at every relapse. Visual field test at the last follow-up showed residual visual field in only a part of the inferior field, and corrected visual acuity was 20/2000.

disease responds to high-dose steroid therapy, but although visual acuity outcome is relatively good, visual field deficits remain, and the lesions tend to recur. This clinical picture suggests that MOG-Ab seropositive disease resembles CRION.

In recent studies, MOG-Abs are measured commonly by cell-based assays.[2,6,13,16–19] Generally, measurement by enzyme-linked immunosorbent assay (ELISA) is influenced by the quantity and property of the protein, which may result in poor quantification and inadequate specificity. On the other hand, cell-based assay is performed by immunohistochemical staining and antigen-antibody reaction can be observed as fluorescence or coloration under a microscope, allowing confirmation of the presence of MOG-Abs. For this reason, we used a cell-based assay in the present study.

In this report and our recent report,[19] we identified two cases double positive for MOG-Abs and anti-AQP4 antibodies. In our past study of 23 cases of optic neuritis, in which we used ELISA to measure MOG-Abs, the positive rates for both MOG-Abs and anti-AQP4 antibodies were higher than the results obtained from cell-based assays, due to false-positive results from ELISA.[6] However, regardless of the method of measurement, double-positive cases were found to have significantly poorer visual outcome, suggesting that anti-AQP4 antibodies and MOG-Abs may indicate the prognosis of visual function in optic neuritis. A recent study has reported that MOG-Ab seropositive patients tend to relapse but respond to treatment better than AQP4-Ab seropositive optic neuritis.[6] Cases positive for MOG-Abs detected by ELISA tend to relapse, have residual visual field deficit, and respond to treatment.

At present, the methods of determining MOG-Abs by cell-based assay have been gradually consolidated in several research groups. Therefore, a standardized method of measuring MOG-Abs should select the cell-based assay in the future.

MOG-Ab seropositive optic neuritis responds to high-dose steroid therapy and plasmapheresis.[15] For AQP4-Ab seropositive cases, since steroid resistance is common, usually two courses of steroid pulse therapy are given, and if visual acuity or visual field does not improve, plasmapheresis is conducted.[20] However, for treatment of neuromyelitis optica, regardless of whether the case is AQP4-Ab seropositive or MOG-Ab seropositive, initial treatment with high-dose steroid therapy is important. Although the pathophysiology of MOG-Abs is unknown, it is clear that the choice of anti-inflammatory and antibody-eliminating treatments is important for optic neuritis. Therefore, in the case of acute onset of optic neuritis, initiating treatment without waiting for the result of MOG-Ab test is appropriate, and clinical diagnosis and characteristic MRI findings become important. In our series, early high-dose steroid therapy and DFPP for acute exacerbation of MOG-Ab seropositive optic neuritis resulted in significant improvement of visual acuity by 2 lines or more in many patients. Therefore, the status of MOG-Abs is highly relevant in deciding treatment strategy and visual outcome.

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REFERENCES

[1] Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;66:1485–1489.

[2] Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 1999;53:1107–1114.

[3] Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004;364: 2106–2112.

[4] Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of opticspinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med* 2005;202:473–477.

[5] Kezuka T. Optic neuritis-immunological approach to elucidate pathogenesis and develop innovative therapy [in Japanese]. *Nihon Ganka Gakkai Zasshi* 2013;117:270–291.

[6] Kezuka T, Usui Y, Yamakawa N, Matsunaga Y, Matsuda R, Masuda M, Utsumi H, Tanaka K, Goto H. Relationship between NMO antibody and MOG-Ab in optic neuritis. *J Neuroophthalmol* 2012;32:107–110.

[7] Rostasy K, Mader S, Schanda K, Huppke P, Gärtner J, Kraus V, Karenfort M, Tibussek D, Blaschek A, Bajer-Kornek B, Leitz S, Schimmel M, Di Pauli F, Berger T, Reindl M. Anti-myelin oligodendrocyte glycoprotein antibodies in pediatric patients with optic neuritis. *Arch Neurol* 2012;69: 752–756.

[8] Shao H, Huang Z, Sun SL, Kaplan HJ, Sun D. Myelin/oligodendrocyte glycoprotein-specific T-cells induce severe optic neuritis in the C57BL/6 mouse. *Invest Ophthalmol Vis Sci* 2004;45:4060–4065.

[9] Kidd D, Burton B, Plant GT, Graham EM. Chronic relapsing inflammatory optic neuropathy (CRION). *Brain* 2003;126:276–284.

[10] Dalton CM, Brex PA, Miszkiel KA, Hickman SJ, MacManus DG, Plant GT, Thompson AJ, Miller DH. Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. *Ann Neurol* 2002;52:47–53.

[11] Tanaka M, Tanaka K. MOG-Abs in adult patients with demyelinating disorders of the central nervous system. *J Neuroimmunol* 2014;270:98–99.

[12] Tanaka K, Tani T, Tanaka M, Saida T, Idezuka J, Yamazaki M, Tsujita M, Nakada T, Sakimura K, Nishizawa M. Antiaquaporin 4 antibody in selected Japanese multiple sclerosis patients with long spinal cord lesions. *Mult Scler* 2007;13:850–855.

[13] Kitley J, Waters P, Woodhall M, Leite MI, Murchison A, George J, Küker W, Chandratre S, Vincent A, Palace J. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. *JAMA Neurol* 2014;71: 276–283.

[14] Tsuburaya RS, Miki N, Tanaka K, Kageyama T, Irahara K, Mukaida S, Shiraishi K, Tanaka M. Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in a Japanese boy with recurrent optic neuritis. *Brain Dev* 2015;37: 145–148.

[15] Ikeda K, Kiyota N, Kuroda H, Sato DK, Nishiyama S, Takahashi T, Misu T, Nakashima I, Fujihara K, Aoki M. Severe demyelination but no astrocytopathy in clinically definite neuromyelitis optica with anti-myelin-oligodendrocyte glycoprotein antibody. *Mult Scler* 2015;21: 656–659.

[16] Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, de Haidar Jorge FM, Takahashi T, Nakashima I, Apostolos-Pereira SL, Talim N, Simm RF, Lino AM, Misu T, Leite MI, Aoki M, Fujihara K. Distinction between MOG antibody seropositive and AQP4 antibody seropositive NMO spectrum disorders. *Neurology* 2014;82:474–481.

[17] Weinshenker BG, Wingerchuk DM. The two faces of neuromyelitis optica. *Neurology* 2014;82:466–467.

[18] Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol* 2007;6:805–815.

[19] Kezuka T, Tanaka K, Matsunaga Y, Goto H. Distinction between MOG antibody seropositive and AQP4 antibody seropositive NMO spectrum disorders. *Neurology* 2014;83: 475–476.

[20] Kitley J, Woodhall M, Waters P, Leite MI, Devenney E, Craig J, Palace J, Vincent A. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. *Neurology* 2012;79: 1273–1277.

症 例 短 報

(神眼 32：280～284, 2015)

3回目の測定で抗AQP4抗体の陽性化を認めた難治性両視神経炎の1例

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A Case of Recurrent Refractory Bilateral Optic Neuritis with Positivity for Anti-AQP4 Antibody at the Third Test

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要 約

3回目の測定で抗AQP4抗体陽性所見が得られた再発性難治性両視神経炎の1例を経験した．52歳女性．前医で両眼視神経炎に対しステロイドパルス療法を施行されたが，再発を認め紹介受診．抗AQP4抗体（CBA法）含め自己抗体は陰性．再発性視神経炎の診断でステロイドパルス療法を施行．その後も再発を繰り返し，両眼の視神経炎の再発を認めた．この時点でも抗AQP4抗体は陰性．5回目の再発時において抗AQP4抗体が陽性を認めた．ステロイドパルス療法は奏功せず血漿交換療法を施行した．NMO spectrum disordersでは抗AQP4抗体の陽転化を認める症例があり，再発を繰り返す難治症例では複数回の測定が望ましい．（神眼32：280～284, 2015）

Abstract

We report the case of a patient with recurrent refractory bilateral optic neuritis who tested negative for anti-aquaporin-4 (AQP4) antibodies until the third test . A 52-year-old woman was referred to us with recurrence of bilateral optic neuritis previously treated by steroid pulse therapy at another hospital. She was negative for autoantibodies including AQP4 antibody (CBA test). She was diagnosed with recurrent optic neuritis and steroid pulse therapy was administered. She subsequently experienced repeated recurrences of optic neuritis affecting both eyes. Anti-AQP4 antibody tests were consistently negative until the fifth recurrence, when the test for this antibody was positive. Because steroid pulse therapy was not effective, plasma exchange was performed instead. Because seroconversion of anti-AQP4 antibody may occur at any time in patients with neuromyelitis optica (NMO) spectrum disorders, this antibody should be measured several times if a patient has refractory optic neuritis with repeated episodes of recurrence.

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Key Words: neuromyelitis optica (NMO), optic neuritis, anti-aquaporin-4 antibody

Ⅰ. 緒言

アクアポリン (AQP) は細胞膜に存在する水チャンネルであり，そのアイソフォームの1つであるAQP4は血液脳関門のアストロサイトに豊富に存在している．このAQP4に対する循環自己抗体が血清に存在し，これを主たる病因として発症する視神経炎は抗AQP4抗体陽性視神経炎と定義されている[1]．抗AQP4抗体陽性視神経炎は，従来NMOの関連疾患NMO spectrum disorder (NMOSD) の一部とみなされていたものであるが，その特徴的な眼症状と予後の重要性から難治性視神経炎の一型として取り扱われている．診断上，抗AQP4抗体陽性所見は診断基準の必須項目であることから，難治性視神経炎で抗AQP4抗体陰性の場合には脱髄性視神経炎，特発性視神経炎，慢性再発性炎症性視神経症など他疾患の可能性を考慮することとなる．抗AQP4抗体陽性視神経炎は，上述の視神経炎と比較して，一般的に，視機能障害が重篤で，再発しやすく，ステロイド治療に抵抗性であることから[1]，治療戦略や予後を鑑みた場合，抗AQP4抗体陽性所見の重要性は際立っている．今回我々は3回目の測定で初めて血中の抗AQP4抗体陽性所見が得られた再発性難治性両視神経炎の1例を経験したので，その詳細な臨床経過を報告する．

Ⅱ. 症例

患者：52歳，女性
既往歴：子宮筋腫
家族歴：特記すべきことなし
嗜好：喫煙10本/日×30年，飲酒焼酎1/2本/日

現病歴：両眼の視力低下，前頭部痛，眼球運動時痛を主訴に近医脳神経外科を受診した．頭部単純MRIは特記する所見を認めず，前医へ紹介受診となった．RV=0.08 (n.c.)，LV=30 cm指数弁．両視神経炎と診断され，ステロイドパルス療法（メチルプレドニゾロン1000 mg×3日間点滴）を施行された．矯正視力は右 (1.5)，左 (1.2) まで改善し，後療法としてプレドニゾロン (PSL) 30 mgの内服が開始された．20 mgまで漸減したところ，再度左眼の視力低下を認め，当院紹介受診となった．

初診時所見：RV=1.5 (n.c.)，LV=0.15 (n.c.)，眼圧：右眼15 mmHg，左眼15 mmHg．

左眼相対性瞳孔求心路障害陽性で，前眼部，中間透光体は特記すべき異常は認めなかった．眼底は，両視神経乳頭の発赤・腫脹を認め，左眼は出血を伴っていた（**図1**）．ゴールドマン視野 (GP) では，左眼はマリオット盲点拡大，中心暗点に加え，周辺部視野狭窄がみられた．右眼はマリオット盲点拡大，傍中心暗点がみられた．（**図2a**）

初診時血液検査所見：WBC，ESR，CRPは正常，抗核抗体 (EIA)，P-ANCA，C-ANCA，抗SS-A抗体，抗SS-B抗体，抗カルジオリピン抗体，抗TPO抗体，抗サイログロブリン抗体の各種自己抗体は陰性，梅毒血清反応は陰性，HSV (CF)，VZV (CF)，CMV (CF) のウイルス抗体価は正常範囲内であった．また，後日判明した抗AQP4抗体の結果は陰性であった．

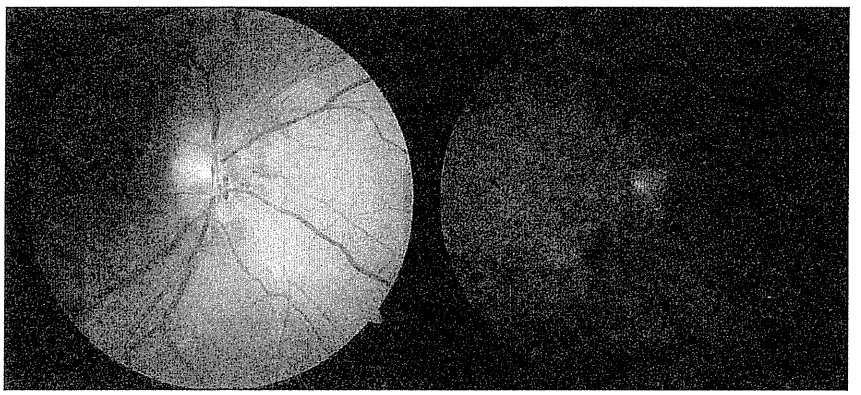
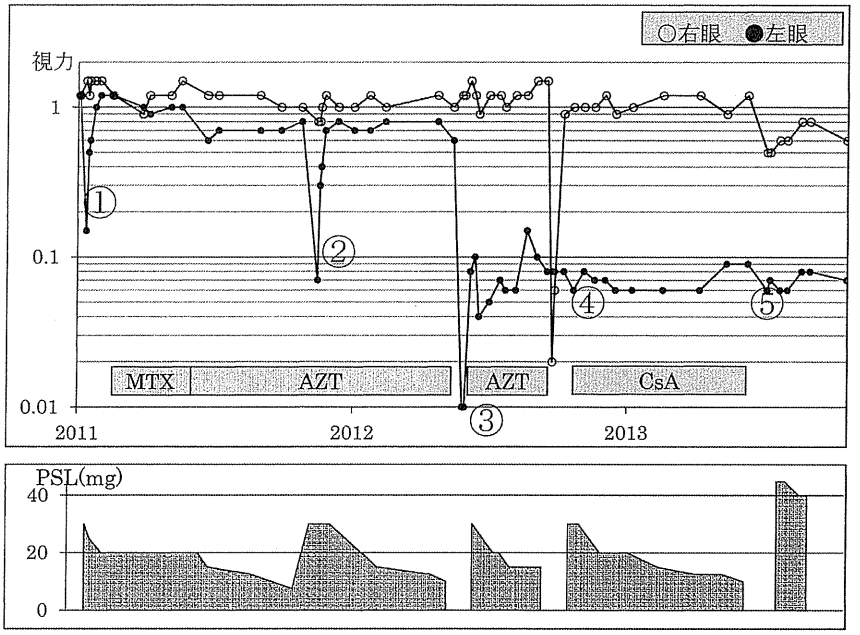


図1：両視神経乳頭の発赤・腫脹を認め，左眼は出血を伴っていた．

表1



初診時画像検査（頭部単純MRI）：脳室周囲や視床下部を含め，頭蓋内に特記すべき所見はみられなかった．

Ⅲ．経過

両視神経炎と診断し，ステロイドパルス療法を開始した（**表1**上矢印）．治療開始後，速やかに眼症状および眼所見の改善が得られ，左眼矯正視力は（1.0）となった．後療法はPSLの内服を30 mg/日から始め．徐々に漸減し，本人の希望もありメトトレキサート（10 mg/週）を併用した．その後，副作用のため，免疫抑制剤をメトトレキサートからアザチオプリン（100 mg/日）へと変更した．

6ヵ月後，両眼の視力低下，頭痛を訴え受診された．矯正視力は右眼0.8，左眼0.07であった．両視神経炎の再発を疑い入院加療を勧めるも，本人の強い希望により外来加療による経過観察となった．頭部単純MRIでは脱髄所見はみられなかった．

5ヵ月後，3度目の左視神経炎の再発を認めた．左眼矯正視力は（10 cm指数弁）となり，GPで中心暗点がみられた（**図2b**）．ステロイドパルスが施行され，中心暗点は縮小し，左眼矯正視力は（0.1）と改善した．

2013年4月，右視神経炎の再発を認め（**図2c**），右眼矯正視力は（0.02）となった．この時点で調べられた抗AQP4抗体は再び陰性であった．ステロイドパルスを2クール行い，右眼矯正視力は（1.0）と改善した．免疫抑制剤をアザチオプリンからシクロスポリン（150 mg/日）内服へ変更し，PSL内服との併用が継続された．この間，左眼の視力およびGP所見は変化を認めなかった．

2014年2月に両視力低下がみられ，両視神経炎の再発と考えられた．この時点で再度抗AQP4抗体を調べたところ陽性所見が得られた．抗AQP4抗体陽性視神経炎と診断し，当院神経内科へ転科後，ステロイドパルスを2クール施行後，血液浄化療法を計7回施行した．治療後，GPにおいて，両眼の中心暗点は残存し（**図2d**），矯正視力は右（0.6），左（0.07）であった．経過中に脊髄炎はみられなかった．

Ⅳ．考案

本症例は，脊髄炎の既往がなく，両眼の視神経炎で発症し，再発を繰り返すなかで，3回目の抗AQP4抗体検査で陽性所見が得られたという点で，過去に報告がない貴重な症例と考えられる．

抗AQP4抗体の陽転化がみられたNMOSDの症例は，過去に2例報告されており，いずれも脊髄炎のみ発症の症例である．Moriらは，9年前の保存血清では抗AQP4抗体が陰性であったが，脊髄炎発症時の血清で陽性化を認めた症例を報告し[7]，長期間にわたる抗体価の上昇がNMOSD発症に関与したと推察してい

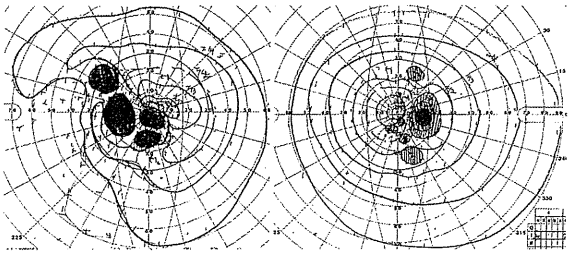


図2a：当院初診時，左眼はマリオット盲点拡大，中心暗点に加え，周辺部視野狭窄がみられた．右眼はマリオット盲点拡大，傍中心暗点がみられた．

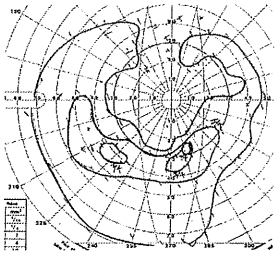


図2b：中心に大きな中心暗点を認めた．

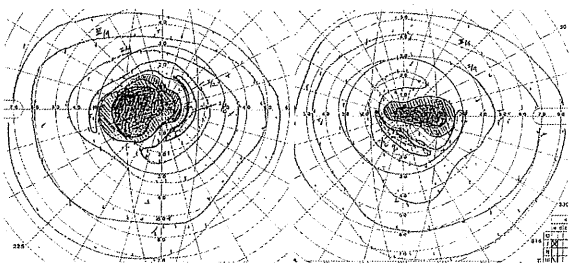


図2c：僚眼である右眼の視神経炎の発症を認めた．

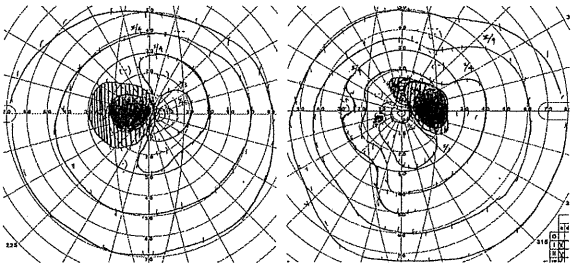


図2d：血漿交換療法後，左眼の中心暗点は残存を認めた．

る．また，Yokoyamaらは，6ヵ月前の保存血清では抗AQP4抗体陰性であったが，脊髄炎発症時の血清で陽性化を認めた症例を報告し[8]，短期間での抗体価の上昇がNMOSD発症に関与した可能性を指摘した．本症例は，一度目の抗AQP4抗体測定はステロイドパルス治療後であり，厳密には上記2例とは異なるが，視神経炎のみ発症のNMOSD（抗AQP4抗体陽性視神経炎）症例であり，一連の経過中の複数回の血液検査で抗AQP4抗体の陽転化がみられたことから，非常に興味深い．

初回および2回目の血液検査で抗AQP4抗体が陰性であった原因としては，初回時については，ステロイドパルス療法後であり，抗体価が一時的に低下していた可能性が，2回目についてはステロイド治療に加え，再発予防に用いたPSL内服や免疫抑制剤が長期にわたり抗体価の上昇を抑えていた可能性，抗体価のカットオフ値などの影響が考えられる．また，CBA法は精度の高い検査であるが，初回および2回目の結果が偽陰性であった可能性も考えられる．その後，抗AQP4抗体が陽転化した原因としては，免疫抑制効果が減弱したこと，疾患活動性が急激に高まったことが考えられるが，抗体価の定量・半定量検査が行われていないことや他の疾患特異的なバイオマーカーがないことから，推測の域を出ない．

抗AQP4抗体測定は，国内では主にAQP4発現細胞を用いた間接蛍光抗体法（cell based assay: CBA）が行われており，本症例の抗AQP4抗体測定もCBA法（東北大学）によって行われた．同一の検体群を複数の方法で測定し，感度・特異度を比較したWatersらの報告では，NMOSDに対する感度は，通常のCBA法が73%，EUROIMMUN社のCBAキットが68%，RSR社のELISA法が60%であった．また特異度に関してはそれぞれ100%であった[9]．抗AQP4抗体検査は2013年11月より保険収載されたが，ELISA法のためCBA法より感度は低い．CBA法は精度の高い抗AQP4抗体測定法であり，特に，東北大のCBA法は感度が85%で，特異度が100%であることから，本症例の報告意義は高いと思われる[10]．以上のことから，診断および予後を考慮したうえでの視神経炎初発時の治療前の抗AQP4抗体測定は重要であると考える．脊髄炎の既往がない視神経炎であっても，NMOSDの可能性を念頭に入れて，抗AQP4抗体は精査すべきであろう．NMOSDでは抗AQP4抗体の陽転化を認める症例があり，再発を繰り返す難治性の視神経炎あるいは脊髄炎症例では複数回の測定が望ましいと考えられた．

利益相反：(無)・有

文 献

1) 抗アクアポリン4抗体陽性視神経炎診療ガイドライン作成委員会：抗アクアポリン4抗体陽性視神経炎診療ガイドライン．日眼会誌 **118**: 419-419, 2014
2) Jacob A, McKeon A, et al: Current concept of neuromyelitis optica (NMO) and NMO spectrum disorders. *J Neurol Neurosurg Psychiatry* **84**: 922-930, 2013
3) Wingerchuk DM: Diagnosis and treatment of neuromyelitis optica. *The neurologist* **13**: 2-11, 2007
4) Wingerchuk DM, Lennon VA, et al: The spectrum of neuromyelitis optica. *The Lancet Neurology* **6**: 805-815, 2007
5) 毛塚剛司：視神経脊髄炎．神経眼科 **31**: 5-12, 2014
6) 病態ごとの治療：視神経脊髄炎多発性硬化症．日本神経学会 日本神経免疫学会 日本神経治療学会（監修）．「多発性硬化症治療ガイドライン」作成委員会（編集）：多発性硬化症治療ガイドライン2010．医学書院，2010
7) Mori M, Kawaguchi N, et al: Seroconversion of anti-aquaporin-4 antibody in NMO spectrum disorder: a case report. *J Neurol* **259**: 980-981, 2012
8) Yokoyama N, Niino M, et al: Seroconversion of neuromyelitis optica spectrum disorder with hyperCKemia: a case report. *Eur J Neurol* **19**: e143, 2012
9) Waters PJ, McKeon A, et al: Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. *Neurology* **78**: 665-671, 2012
10) Sato DK, Nakashima I, et al: Aquaporin-4 antibody-positive cases beyond current diagnostic criteria for NMO spectrum disorders. *Neurology* **80**: 2210-2216, 2013