

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/301483676>

Autoantibodies to neural antigens in CNS demyelinating disorders

Article · January 2016

DOI: 10.4172/0975-9042.000108

CITATIONS

0

READS

16

2 authors, including:



[Takayuki Kondo](#)

Kyoto University

51 PUBLICATIONS 2,383 CITATIONS

SEE PROFILE

All content following this page was uploaded by [Takayuki Kondo](#) on 30 June 2016.

The user has requested enhancement of the downloaded file. All in-text references [underlined in blue](#) are added to the original document and are linked to publications on ResearchGate, letting you access and read them immediately.

Autoantibodies to neural antigens in CNS demyelinating disorders.

Mitsuru Watanabe^{1,2}, Takayuki Kondo^{1,3*}

¹Department of Neurology, Kitano Hospital Medical Research Institute, 2-4-20 Ohgimachi, Kita-ku, Osaka, 530-8480, Japan

²Department of Neurology, Neurological Institute, Kyushu University Graduate School of Medicine, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan

³Department of Community Network and Collaborative Medicine, Kyoto University Hospital, 54 Kawaharacho Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan

Abstract

The relationship between central nervous system demyelinating disorders (CNSDDs) and anti-neural antibodies (Abs), with the exception of anti-aquaporin 4 (AQP4) Abs, is not well understood. We previously screened for a variety of anti-neural Abs in the sera of Japanese patients with CNSDDs and found three patients with anti-N-methyl-D-aspartate receptor (NMDAR) Abs and three patients with anti-contactin-associated protein 2 (CASPR2) Abs. These Abs have not yet been considered as causing CNSDDs. Here, we describe CNSDD patients with these autoantibodies and discuss whether these Abs are pathogenic or not, based on the clinical presentation and literature documentation. Moreover, we propose points to which attention should be paid when dealing with patients with CNSDDs in a clinical setting.

Accepted February 10, 2016

Introduction

It is assumed that central nervous system demyelinating disorders (CNSDDs), such as multiple sclerosis (MS) and neuromyelitis optica (NMO) spectrum disorders (NMOSDs), are autoimmune disorders. While the autoaggressive role of T cells has been well documented in MS, NMOSDs are currently thought to be antibody-mediated disorders. However, the concept that MS and NMOSDs are distinct disorders was not confirmed until NMO-IgG or anti-aquaporin 4 (AQP4) antibodies (Abs) were discovered in patients with NMOSDs [1,2]. The discovery of NMO-IgG has also overturned the hypothesis that the target antigens in CNSDDs are necessarily myelin and/or oligodendrocytes. Hence, searching for anti-neural Abs in CNSDDs may provide information crucial to understanding the pathogenesis of each patient and finding clues for classifying the heterogeneous CNSDDs.

We previously screened for a variety of anti-neural Abs in the sera of Japanese patients with CNSDDs [3]. In this mini review, we try to describe the association between CNSDDs and anti-neural antibodies based on our findings and the reports of other groups.

Anti-neural antibodies in CNSDD patients

Seventy patients with CNSDDs were enrolled in our study, of which 29 had MS, 28 had NMO/NMOSDs, and 13 had clinically isolated syndrome (CIS). We searched

the sera of the patients for Abs against the following antigens: AQP4, glutamate receptors (*N*-methyl-D-aspartate receptor (NMDAR) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) types), contactin-associated protein 2 (CASPR2), leucine-rich glioma-inactivated protein 1 (LGI1), glutamic acid decarboxylase (GAD), myelin associated glycoprotein (MAG), γ -aminobutyric acid B receptor (GABA_BR), glycine receptor (GlycineR), CV2, amphiphysin, Hu, Ri, Yo, Tr, Ma2, and myelin. Anti-AQP4 Abs were detected in 24 patients with NMO/NMOSDs. Anti-NMDAR Abs were detected in two patients with NMO/NMOSDs and one with MS. Anti-CASPR2 Abs were detected in two patients with NMO/NMOSDs and one with CIS. Only one of the three patients with anti-CASPR2 Abs was positive for anti-AQP4 Abs. We detected anti-Ma2 Abs in one patient with MS and anti-Tr Abs in another MS patient. Anti-myelin Abs were detected in sera from two patients from each of the three groups. Other anti-neural Abs were not detected in any of the patients [3].

Similar to our report, Hacoen et al. tested autoantibodies to astrocyte, myelin, and neuronal antigens in sera of 65 children with CNSDDs. Fifteen patients (23%) were positive for at least one Ab. Anti-AQP4 Abs and anti-myelin oligodendrocyte glycoprotein (MOG) Abs were detected in three and seven patients, respectively. Anti-NMDAR Abs were found in one monophasic acute disseminated encephalomyelitis (ADEM) patient and one additional

patient with optic neuritis, who was also positive for anti-VGKC-complex Abs. Anti-VGKC-complex Abs were also found in a patient with monophasic ADEM and a patient with relapsing-remitting MS (RRMS). Anti-GlycineR Abs were detected in a patient with transverse myelitis. The authors discussed the possibility that these autoantibodies can be pathogenic and result in CNS demyelination or contribute to the accompanying disability, but their clinical relevance remained unclear [4].

In this review, we focus on the association of anti-NMDAR Abs and anti-CASPR2 Abs with CNSDDs. Additionally, we describe patients with multiple autoantibodies to assess whether the presence of each antibody is necessarily pathogenic or not.

i) CNSDD patients with anti-NMDAR antibodies

Anti-NMDAR Abs are usually detected in anti-NMDAR encephalitis patients who develop a clinical syndrome characterized by acute behavioral changes, dyskinesia, seizures, a decrease in consciousness, psychosis, and/or autonomic dysregulation [5]. However, findings suggest that patients with anti-NMDAR Abs may have demyelinating lesions. According to a report by Titulaer et al., 23 out of 691 patients (3.3%) with anti-NMDAR encephalitis had MRI and/or clinical features of CNSDDs, and five patients had only anti-NMDAR Abs, but not anti-AQP4 Abs nor anti-MOG Abs [6]. In our study, a 39-year-old man diagnosed with MS had anti-NMDAR Abs. He had two episodes of hemisensory disturbance on his left side and dizziness caused by brainstem and cerebral lesions [3]. Waschbisch et al. also reported a 33-year-old male patient with clinically definite MS who was found to be positive for anti-NMDAR Abs. This patient had rituximab therapy and was clinically stable for 18 months of follow-up. He was carefully evaluated for typical signs of anti-NMDAR encephalitis, such as seizures, dyskinesia, and psychiatric or neuropsychological symptoms, all of which were negative [7]. Another case report showed a Japanese girl with recurrent optic neuritis and transient cerebral lesions who was positive for anti-NMDAR Abs [8]. These patients with anti-NMDAR Abs only showed symptoms relating to CNSDDs, but not to anti-NMDAR encephalitis. It has also been reported that white matter changes, which are indicative of demyelination, are also visible in anti-NMDAR encephalitis patients by using diffusion tensor imaging and resting functional MRI. This fact suggests that myelin disruption is more common in anti-NMDAR Ab positive cases than was suspected based on clinical grounds or on conventional MRI [9]. Taken together with the fact that oligodendrocytes contain NMDAR [10], anti-NMDAR Abs could play a role in the demyelinating process in anti-NMDAR Ab positive patients. However, there is also the possibility that anti-NMDAR Abs do not contribute to the formation of demyelinating lesions and that the coexisting autoimmunity against different targets plays a more crucial role in demyelination. Thus, further

studies are required in order to determine whether anti-NMDAR Abs themselves induce demyelination or not.

Ramberger et al. also recently analyzed anti-NMDAR Abs in 215 patients with CNSDDs (including 51 patients with ADEM, 41 with NMOSDs, 34 with CIS, and 89 with MS), and found only one RRMS patient who was positive for anti-NMDAR Abs. This patient had anti-NMDAR Abs at the onset of MS and, 3 years later, developed anti-NMDAR encephalitis-related symptoms, which include psychiatric (dysphoria, logorrhea) and cognitive symptoms (dyscalculia, frontal executive disorder, psychomotor slowing) [11]. There is another case report, which presents an MS patient with anti-NMDAR Abs who has clinical characteristics not only of MS, but also of anti-NMDAR encephalitis. The patient developed severe cognitive impairment associated with anti-NMDAR Abs after the typical clinical course of RRMS [12]. Thus, serum anti-NMDAR Abs could be a susceptible marker for an overlapping anti-NMDAR encephalitis-related disease course in patients with CNSDDs. In other words, anti-NMDAR encephalitis may develop in CNSDD cases with anti-NMDAR Abs, but without any relevant episodes of anti-NMDAR encephalitis.

Anti-NMDAR Abs are not frequently detected in CNSDD patients, but it should be noted that anti-NMDAR Abs may be more prevalent than previously considered, and they can be related to the CNSDD or can be a suggestive marker that will cause an anti-NMDAR encephalitis-relevant episode later.

ii) CNSDD patients with anti-CASPR2 antibodies

CASPR2 is localized on myelinated axons in the juxtapanodal region in the CNS and the peripheral nervous system and is one of the VGKC-complex-associated proteins. To date, anti-CASPR2 Abs have been reported to be associated with limbic encephalitis, Morvan's syndrome, acquired neuromyotonia, and nonparaneoplastic cerebellar ataxia [13]. Our study first detected anti-CASPR2 Abs in three CNSDD patients, namely, two NMO/NMOSD patients and one CIS patient. One NMO/NMOSD patient also had anti-AQP4 Abs, but the other two only carried anti-CASPR2 Abs; in other words, no other responsible Abs other than anti-CASPR2 Abs were identified. Moreover, the distribution of the lesions was common to these three patients, and was limited to the brainstem or the spinal cord [3]. Our observation is partly consistent with a report that found VGKC-complex targeted immunity in some child demyelinating disorders and suggested its possible relationship to demyelination; however, anti-CASPR2 Abs themselves were not found in this study [4].

The presence of anti-CASPR2 Abs in Asian patients with presumed autoimmune neurological disorders was investigated in Korea. Of 1820 patients, five patients were positive for anti-CASPR2 Abs, but none of them showed any episodes or had MRI findings indicative of CNSDDs

[13]. Therefore, it has not been elucidated whether anti-CASPR2 Abs induce CNSDDs.

Additionally, a report showed that some limbic encephalitis patients with anti-VGKC complex Abs exhibited a specific MRI feature – an increased T2 signal of the supratentorial white matter. Although this MRI finding is compatible with hypomyelination rather than demyelination, this may indicate the potential of anti-LGI1 and anti-CASPR2 Abs to induce structural myelin change [14].

iii) CNSDD patients with multiple types of autoantibodies

In our study, there were three patients with multiple types of autoantibodies against neural antigens. Of these three patients, two had both anti-AQP4 and anti-NMDAR Abs, and one had both anti-AQP4 and anti-CASPR2 Abs [3]. The relationship of anti-CASPR2 Abs and CNSDDs has already been discussed. Here, we discuss the patients with both anti-AQP4 and anti-NMDAR Abs. One of these patients was a 34-year-old woman who had not only a history of intractable hiccups, optic neuritis, tetraplegia, sensory disturbance, and bladder and bowel disturbance compatible with an episode of NMO, but also had an episode of delirium, hallucination and generalized seizure compatible with an episode of anti-NMDAR encephalitis. On the other hand, the other patient with both anti-AQP4 and anti-NMDAR Abs had only multiple episodes of myelitis, but had no episodes of anti-NMDAR encephalitis.

In a study by Titulaer et al., among 691 patients with anti-NMDAR encephalitis, nine patients had both anti-NMDAR and anti-AQP4 Abs, and nine patients had both anti-NMDAR and anti-MOG Abs. Of the anti-NMDAR and anti-AQP4 Ab positive patients, four patients had an NMOSD, which was similar to our case, three patients had only atypical symptoms, such as ataxia or facial and bulbar palsy, and two had no symptoms indicative of NMOSDs [6].

Considering these reports, there are rare cases of patients with both anti-AQP4 and anti-NMDAR Abs who also have episodes of both NMO/NMOSDs and anti-NMDAR encephalitis. This fact suggests that more than one anti-neural autoantibody type can participate in CNS pathogenesis in a single patient. Therefore, in the case of patients who have a CNSDD with unusual symptoms (e.g. psychiatric manifestations, seizures, memory deficits, autonomic instabilities, etc.), the possibility of them having anti-NMDAR encephalitis should be considered, and vice versa in patients with anti-NMDAR encephalitis, who could also have a CNSDD. On the other hand, some patients with both anti-AQP4 and anti-NMDAR Abs had either episodes of NMO/NMOSDs or anti-NMDAR encephalitis. These cases may show that not all of the detected autoantibodies are necessarily pathogenic.

A similar case report was published in 2013. A middle-aged woman, whose serum harbored anti-NMDAR and anti-AQP4 Abs, developed limbic encephalitis followed by NMO [15].

We have to keep in mind that patients with both anti-AQP4 and anti-NMDAR Abs, one of which could be clinically silent at a certain moment, may develop a CNSDD or anti-NMDAR encephalitis in the future.

Discussion

Many anti-neural Abs have been reported to be related to or induce CNSDDs so far. In our previous report, we screened for a variety of anti-neural Abs in the sera of Japanese patients with CNSDDs and found that some CNSDD patients had anti-NMDAR Abs or anti-CASPR2 Abs [3], neither of which are usually considered a cause of CNSDDs. So we focused on anti-NMDAR Abs and anti-CASPR2 Abs in this review. However, it remains an open question whether the existence of anti-NMDAR or anti-CASPR2 Abs is associated with demyelination or if other unclarified autoimmune mechanisms play a role in demyelination, because our previous findings were just based on the fact that some CNSDD patients had such anti-neural Abs in their sera. At the same time, these Abs may indicate the presence of overlapping syndromes of CNSDDs and other CNS autoimmune diseases, such as anti-NMDAR encephalitis. There is also the possibility that they are not pathogenic in CNSDDs or they are responsible for some pathogenic processes but not that of demyelination.

Although it might be interpreted that more than one distinct autoimmune CNS disease developed independently in a single person by chance or due to autoimmune-prone conditions, extended autoimmunity against multiple neural antigens may result from the release of neural antigens after tissue damage caused by inflammation and/or demyelination in the CNS (i.e. epitope spreading). This etiology is consistent with the report that children with relapsing MS had autoantibodies against a broader range of CNS antigens more often than children with monophasic demyelinating disorders [16]. However, the exact mechanisms remain unknown. To clarify the relationship between anti-neural Abs and CNSDDs, much larger clinical studies that include much more patients with such anti-neural Abs are needed and the clinical characteristics of such patients should be reported. Moreover, new anti-neural Abs, which are more specific and directly pathogenic for CNS, could be discovered in the future, so we have to keep searching such Abs. In addition to clinical studies, basic experiments such as cell culture or animal model experiments are awaited to show the pathogenicity of antibodies and show the detailed mechanisms.

In a clinical setting, we recommend considering the possibility that unidentified or undetected Abs can present and be pathogenic in CNSDD patients, especially when the symptoms are not typical, even if some Abs have already been detected. If some autoantibodies are detected, it should be carefully considered whether the Abs are pathogenic or not, and the patients should be followed up with attention.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or non-profit sectors.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

References

1. 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.
2. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin 4 water channel. *J Exp Med*. 2005; 202:473-477.
3. Watanabe M, Kondo T, Murakata K, Kageyama T, Shibata Y, Takahashi T, Nomura K, Matsumoto S. Antibodies to neural and non-neural autoantigens in Japanese patients with CNS demyelinating disorders. *J Neuroimmunol*. 2014; 274:155-160.
4. Hacohen Y, Absoud M, Woodhall M, Cummins C, De Goede CG, Hemingway C, Jardine PE, Kneen R, Pike MG, Whitehouse WP, Wassmer E, Waters P, Vincent A, Lim M; UK & Ireland Childhood CNS Inflammatory Demyelination Working Group. Autoantibody biomarkers in childhood-acquired demyelinating syndromes: results from a national surveillance cohort. *J Neurol Neurosurg Psychiatry*. 2014; 85:456-461.
5. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008; 7:1091-1098.
6. Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, Benson LA, Shu H, Irioka T, Hirano M, Singh G, Cobo Calvo A, Kaida K, Morales PS, Wirtz PW, Yamamoto T, Reindl M, Rosenfeld MR, Graus F, Saiz A, Dalmau J. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014; 75:411-428.
7. Waschbisch A, Kallmünzer B, Schwab S, Gölitz P, Vincent A, Lee DH, Linker RA. Demyelinating disease and anti-N-methyl-D-aspartate receptor immunoglobulin G antibodies: a case report. *BMC Res Notes*. 2014; 7:948.
8. Ishikawa N, Tajima G, Hyodo S, Takahashi Y, Kobayashi M. Detection of autoantibodies against NMDA-type glutamate receptor in a patient with recurrent optic neuritis and transient cerebral lesions. *Neuropediatrics*. 2007; 38:257-260.
9. Finke C, Kopp UA, Scheel M, Pech LM, Soemmer C, Schlichting J, Leypoldt F, Brandt AU, Wuerfel J, Probst C, Ploner CJ, Prüss H, Paul F. Functional and structural brain changes in anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2013; 74:284-296.
10. Lipton SA. NMDA receptors, glial cells, and clinical medicine. *Neuron*. 2006; 50:9-11.
11. Ramberger M, Bsteh G, Schanda K, Höftberger R, Rostásy K, Baumann M, Aboulenein-Djamshidian F, Lutterotti A, Deisenhammer F, Berger T, Reindl M. NMDA receptor antibodies: A rare association in inflammatory demyelinating diseases. *Neurol Neuroimmunol Neuroinflamm*. 2015; 2:e141.
12. Fleischmann R, Prüss H, Rosche B, Bahnemann M, Gelderblom H, Deuschle K, Harms L, Kopp U, Ruprecht K. Severe cognitive impairment associated with intrathecal antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor in a patient with multiple sclerosis. *JAMA Neurol*. 2015; 72:96-99.
13. Sunwoo JS, Lee ST, Byun JI, Moon J, Shin JW, Jeong DE, Lee GH, Jeong SH, Shin YW, Jung KH, Lee DY, Jeon D, Jung KY, Kim M, Lee SK, Chu K. Clinical manifestations of patients with CASPR2 antibodies. *J Neuroimmunol*. 2015; 281:17-22.
14. Urbach H, Rauer S, Mader I, Paus S, Wagner J, Malter MP, Prüss H, Lewerenz J, Kassubek J, Hegen H, Auer M, Deisenhammer F, Ufer F, Bien CG, Baumgartner A. Supratentorial white matter blurring associated with voltage-gated potassium channel-complex limbic encephalitis. *Neuroradiology*. 2015; 57:1203-1209.
15. Zoccarato M, Saggi MV, Serra G, Pelizza MF, Rosellini I, Peddone L, Ticca A, Giometto B, Zuliani L. Aquaporin-4 antibody neuromyelitis optica following anti-NMDA receptor encephalitis. *J Neurol*. 2013; 260:3185-3187.
16. Quintana FJ, Patel B, Yeste A, Nyirenda M, Kenison J, Rahbari R, Fetco D, Hussain M, O'Mahony J, Magalhaes S, McGowan M, Johnson T, Rajasekharan S, Narayanan S, Arnold DL, Weiner HL, Banwell B, Bar-Or A; Canadian Pediatric Demyelinating Disease Network. Epitope spreading as an early pathogenic event in pediatric multiple sclerosis. *Neurology*. 2014; 83:2219-2226.

Correspondence to:

Takayuki Kondo,

Department of Community Network and Collaborative Medicine,

Kyoto University Hospital,
54 Kawaharacho Shogoin, Sakyo-ku,
Kyoto, 606-8507, Japan.

e-mail: takakon78@hotmail.com

Tel.: +81 75 751 3110,

Fax: +81 75 751 3115