Journal of Neuroimmunology 330 (2019) 35–37

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

A case of treatable dementia with Lewy bodies remarkably improved by immunotherapy

Kie Abe, Yuhei Chiba*

Department of Psychiatry, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-Ku, Yokohama-Shi, Kanagawa-Ken 236-0004, Japan

ARTICLE INFO

Keywords:
Dementia with Lewy bodies
Autoimmune encephalitis
Treatable dementia
Neuroinflammation
Anti-*N*-methyl-D-aspartic acid receptor antibody
Anti-thyroid antibody

ABSTRACT

We report a case of probable dementia with Lewy bodies (DLB) with several findings indicating autoimmune encephalitis (e.g. anti-thyroid antibodies in serum and oligoclonal band and anti-*N*-methyl-D-aspartic acid receptor antibodies in cerebrospinal fluid). The symptoms and the findings of ancillary tests such as Iodine-123-metaiodobenzylguanidine myocardial scintigraphy and ^{99m}Technetium-ethyl-cysteinate-dimer single photon emission computed tomography were improved after the pulse and oral steroid treatment. This case is thought the autoimmune encephalitis mimicking DLB. This experience indicated the importance of suspecting treatable DLB even when the findings of laboratory and radiological tests fulfill the diagnostic criteria of DLB.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common types of degenerative dementia characterized by progressive dementia, visual hallucinations, Parkinsonism, cognitive fluctuations, and rapid eye movement (REM) sleep behavior disorder. The pathologic hallmark of DLB is the presence of Lewy pathology consisting of α-synuclein. The clinical diagnosis is indicated by reduced cardiac Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) uptake and reduced dopamine transporter uptake in basal ganglia demonstrated by single photon emission computed tomography (DaT-SPECT) and supported by hypoperfusion in occipital lobe demonstrated by SPECT. (Mckeith et al., 2017).

Autoimmune encephalitis has recently been recognized as a cause of treatable dementia. (Mckeon et al., 2010; Flanagan et al., 2016) Autoimmune encephalitis is suspected when a patient exhibits subacute onset, new focal central nervous system (CNS) signs, cerebrospinal fluid (CSF) pleocytosis or brain magnetic resonance imaging (MRI) abnormalities. (Graus et al., 2016)

Although the potential role of neuroinflammation in the pathogenesis of neurodegenerative disease including Alzheimer's disease has received great attention in recent years, the significance of neuroinflammation in DLB is still unknown. (Surendranathan et al., 2015) Here, we report a case of probable DLB whose symptoms and findings of ancillary tests were remarkably improved after immunotherapy.

2. Material and methods

A case report. The written informed consent for reporting was obtained from the subject.

3. Results

The subject is a 64-year-old Japanese female. She was diagnosed with lymphocytic posterior pituitary colitis (LPPC), which had been well-controlled with the normal serum sodium level by a hormonal treatment during the whole follow-up period.

Two months after the onset of LPPC, she started to exhibit anxiety and agitation. Anti-anxiety and anti-depressant drugs were partially effective. She gradually developed visual hallucination, disinhibition, emotional instability, sleep disorder and cognitive impairment such as disorientation, memory disturbance, loss of attention and cognitive fluctuation. Therefore, she was referred to the Department of Psychiatry at our hospital about one year after the onset of psychiatric symptoms.

The evaluation of neuropsychiatric symptoms and the findings of ancillary tests at the first examination are summarized in Table 1 and in the graphical abstract. She exhibited moderate dementia accompanied by visual hallucination, severe anxiety, and disinhibition, which got worse especially at night. Her sleep-wake rhythm was irregular, and aggressive behavior was often observed at night. She exhibited Parkinsonism such as speech disorder, gait disorder, rigidity in bilateral elbow joints, resting tremor, clumsy finger tapping, hand movement, and dysdiadochokinesis. She also exhibited severe constipation. She

* Corresponding author.
E-mail address: suezan_2000@yahoo.co.jp (Y. Chiba).

https://doi.org/10.1016/j.jneuroim.2019.02.003
Received 20 December 2018; Received in revised form 26 January 2019; Accepted 10 February 2019

Table 1
Changes in the neuropsychiatric symptoms and the findings of the ancillary tests during the follow-up period.

		Before	1st year	2nd year	3rd year	4th year
Psychiatric symptoms	BPRS	70	53	28	18	18
	NPI-12	116	47	22	N/A	8
Cognitive function	MMSE	19	12	22	27	27
General function	mRS	5	3	2	0	0
Parkinsonism	UPDRS-III	39	43	3	0	0
CSF findings	Cell (/μl)	2	0	N/A	N/A	N/A
	Protein (mg/dl)	31	27	N/A	N/A	N/A
	IgG index [< 0.6]	0.64	0.88	N/A	N/A	N/A
	OCB [negative]	positive	Negative	N/A	N/A	N/A
	Anti-NR1 (OD)	0.830	0.307	N/A	N/A	N/A
	Anti-NR2B (OD)	0.620	0.236	N/A	N/A	N/A
MRI	Atrophy	bilateral MTL	bilateral MTL	Bilateral MTL	N/A	Bilateral MTL
	WMH	None	None	None	N/A	None

The evaluation of neuropsychiatric symptoms and the findings of the ancillary tests at the first examination and during the follow-up period are summarized. The units are shown in round brackets. The normal limits and the cut-off values are shown in square brackets.
Before; before the immunotherapy, 1st to 4th year; The first to the fourth year after the immunotherapy, CSF findings, cerebrospinal; MRI, magnetic resonance imaging; BPRS, Brief Psychiatric Rating Scale; NPI-12, Neuropsychiatry Inventory-12; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; OCB, Oligoclonal band; Ab, antibody; MTL, medial temporal lobe; WMH, white matter hyperintensity; N/A, not applicable, BPRS ranges from 18 to126. NPI ranges from 0 to 144. The higher the score of BPRS and NPI, the worse the symptoms.

needed watch and support at all time.

The following radiological tests and the laboratory tests were performed within a month after the admission. The findings of physical examination, X-ray of chest, general blood test showed no abnormalities. Opportunistic infection, metabolic abnormalities, endocrine dysfunction or drug-induced disorders were excluded. Anti-thyroglobulin (anti-TG) antibody was elevated in serum (70.7 IU/ml: normal limit < 28 IU/ml). Other autoantibodies including anti-nuclear, anti-DNA, anti-double strand DNA, anti-SM, anti-RNP, anti-SS-A, anti-SS-B, anti Sc170, anti-phospholipid, proteinase-3 anti-neutrophil cytoplasmic and myeloperoxidase anti-neutrophil cytoplasmic antibodies were found all negative.

The MRI of her brain showed mild atrophy in the bilateral medial temporal lobe but no white matter hyperintensities. The ^{99m}Technetium-ethyl-cysteinate-dimer (ECD) SPECT exhibited hypoperfusion in the bilateral occipital lobe. DaT-SPECT revealed a slight asymmetrical pattern with specific binding ratios of 8.31 (right) and 8.24 (left). ^{123}I-MIBG scintigraphy demonstrated decreased myocardial uptake and increased wash out ratio. Her night-time behavior might originate from RBD, but we could not perform the polysomnography due to psychiatric symptoms. These clinical and radiological findings met the criteria for probable DLB.

The response to the general psychiatric treatments including anti-anxiety, anti-depressant and anti-psychotics was insufficient, we, therefore, stopped administering them except valproate, which was relatively effective for her disinhibition. Because of subacute onset, comorbid autoimmune pituitary colitis, detection of anti-thyroid antibody, we performed a lumbar puncture. The Cell count, the total protein and the glucose in cerebrospinal fluid (CSF) were normal. IgG index was slightly elevated (0.64). Oligoclonal band (OCB) was found positive, and enzime-linked immunosorbent (ELIS) assayed IgG antibodies against *N*-methyl-D-aspartic acid (NMDA) receptor subunit NR1 and NR2B were detected. (Fukuyama et al., 2015) We, therefore, performed pulse steroid treatment (methylprednisolone 1000 mg/day intravenous for three days) and started post-pulse steroid treatment (methylprednisolone 10 mg/day oral).

No obvious change was observed in the first month after the immunotherapy. She was therefore transferred to a local psychiatric hospital. During the first year after the pulse steroid treatment, her behavioral and psychiatric symptoms were slightly improved, while cognitive dysfunction deteriorated to the severe dementia level and the motor dysfunction was exacerbated. The CSF examination revealed that the anti-NR1 and anti-NR2B antibody titers decreased and OCB became negative. Improvement of behavioral and psychiatric symptoms and an introduction of at-home nursing care services enabled her to go back home.

Three years after the immunotherapy, her cognitive function was restored to the normal level. Neuropsychiatric symptoms and Parkinsonism completely disappeared, and she was no longer in need of help for daily activities and housework. She did not even fulfill the diagnostic criteria of possible DLB. We finally stopped administering methylprednisolone.

Although she still exhibits constipation and mild insomnia four years after the immunotherapy, no recurrence of neuropsychiatric symptoms or movement disorder has been observed. The ECD-SPECT hypoperfusion in occipital lobe became mild, myocardial uptake in ^{123}I-MIBG scintigraphy was remarkably restored and wash out ratio was also improved. The changes in the clinical symptoms and the findings of tests are summarized in Table 1.

4. Discussion

The clinical features and the radiological findings of the subject fulfilled the diagnostic criteria of probable DLB. (Mckeith et al., 2017) However, detection of anti-NMDA receptor antibody, anti-thyroid antibody and OCB and remarkable improvement after immunotherapy rather supported the diagnosis of autoimmune encephalitis. (Graus et al., 2016) Ikura et al. reported a similar case of probable DLB who was also suspected of having autoimmune encephalitis because of anti-thyroid antibodies, anti-*N*-terminal of alpha-enolase antibodies and ELIS assayed anti-NMDA receptor antibodies. (Ikura et al., 2015) Coban et al. also reported a similar case of probable DLB with cell-based assayed anti-NMDA receptor antibody, who rapidly recovered after immunotherapy. (Coban et al., 2014) These 3 cases are compared in Supplementary Table 1. The novelty of the present report is that the improvement of the global cerebral hypoperfusion and myocardial uptake in ^{123}I- MIBG scintigraphy was confirmed after the immunotherapy.

In the present case, the cognitive function was improved to obtain 27 points on MMSE, visual hallucination and Parkinsonism disappeared. The remaining features of the present case, constipation and occipital hypoperfusion, do not fulfill the criteria of possible DLB. (Supplementary Table 2.) Considering that constipation is a non-specific feature and her current insomnia is not accompanied by behavioral disorder, the present case currently lacks the characteristics of Lewy body disease. A recent study showed that the patients with anti-NMDA receptor encephalitis sometimes shows occipital hypoperfusion. (Probasco et al., 2018) Therefore, the present case can not necessarily

be considered as a Lewy body disease based on the SPECT hypoperfusion in the occipital lobe.

The present case indicates a possibility that the immune system is related with the development of characteristic features of DLB. Surendranathan et al. reviewed the evidence of microglial activation induced by α-synuclein observed years before neuronal death in Lewy body diseases. (Surendranathan et al., 2015) King et al. reported that peripheral inflammation occurs in the prodromal stage of DLB. (King et al., 2018) On the other hand, previous studies reported that the SPECT hypoperfusion in the occipital lobe (Probasco et al., 2018) and RBD (Iranzo et al., 2006) are frequently observed in a subpopulation of autoimmune encephalitis. There is also a report on the reduction of myocardial uptake in ^{123}I- MIBG scintigraphy in a case of herpes simplex virus encephalitis (Kikumoto et al., 2018)

In the present case, it might be possible that comorbid inflammatory diseases such as LPPC and autoimmune encephalitis triggered neuroinflammation leading to the characteristics of DLB. Moreover, the remarkable improvement of the clinical symptoms and the biomarkers after the immunotherapy imply a possibility that neuroinflammation itself might induce DLB symptoms rather than due to neurodegeneration. Delirium often occurs months or years prior to dementia in about a quarter of DLB patients compared to only 7% of cases with Alzheimer's disease. (Mckeith et al., 2016) Inflammation surrounding both delirium and DLB would be an interesting area for future research. (Gore et al., 2015) The existence of relationships between the neuroinflammation and the development of specific features of DLB would attract attention. (Fujishiro, 2018)

5. Conclusion

We reported a patient who exhibited the characteristic symptoms and test findings of DLB, which were remarkably improved after the immunotherapy. This experience indicated the importance of suspecting treatable DLB even when the diagnostic criteria of DLB was fulfilled. This case report lacks the pathological investigation and the evaluation of the several kinds of other autoantibody-mediated autoimmune encephalitis. Accumulation of studies is necessary for further understanding of the relationship between the immune system and development of DLB features.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2019.02.003.

Declarations of interest

None.

Funding

This work was partially supported by JSPS KAKENHI Grant Number JP17K16390.

References

Coban, A., Ismail Kucukali, C., Bilgic, B., Yalcinkaya, N., Haytural, H., Ulusoy, C., Turan, S., Cakir, S., Ucok, A., Unubol, H., Hanagasi, H.A., Gurvit, H., Tuzun, E., 2014. Evaluation of incidence and clinical features of antibody-associated autoimmune encephalitis mimicking dementia. Behav. Neurol. 2014, 935379.

Flanagan, E.P., Drubach, D.A., Boeve, B.F., 2016. Autoimmune dementia and encephalopathy. Handb. Clin. Neurol. 133, 247–267.

Fujishiro, H., 2018. Neuroinflammation as a potential therapeutic target in dementia with Lewy bodies. J. Neurol. Neurosurg. Psychiatry 89, 328.

Fukuyama, T., Takahashi, Y., Kubota, Y., Mogami, Y., Imai, K., Kondo, Y., Sakuma, H., Tominaga, K., Oguni, H., Nishimura, S., 2015. Semi-quantitative analyses of antibodies to N-methyl-d-aspartate type glutamate receptor subunits (GluN2B & GluN1) in the clinical course of Rasmussen syndrome. Epilepsy Res. 113, 34–43.

Gore, R.L., Vardy, E.R., O'brien, J.T., 2015. Delirium and dementia with Lewy bodies: distinct diagnoses or part of the same spectrum? J. Neurol. Neurosurg. Psychiatry 86, 50–59.

Graus, F., Titulaer, M.J., Balu, R., Benseler, S., Bien, C.G., Cellucci, T., Cortese, I., Dale, R.C., Gelfand, J.M., Geschwind, M., Glaser, C.A., Honnorat, J., Hoftberger, R., Iizuka, T., Irani, S.R., Lancaster, E., Leypoldt, F., Pruss, H., Rae-Grant, A., Reindl, M., Rosenfeld, M.R., Rostasy, K., Saiz, A., Venkatesan, A., Vincent, A., Wandinger, K.P., Waters, P., Dalmau, J., 2016. Lancet Neurol. 15, 391–404 A clinical approach to diagnosis of autoimmune encephalitis.

Ikura, T., Fujishiro, H., Takahashi, Y., Yoneda, M., Saito, T., Chiba, Y., Kamada, A., Katsuse, O., Hirayasu, Y., 2015. A patient with probable dementia with Lewy bodies and positive autoantibodies against the Anti-NH < sub > 2 < /sub > -terminal of α-Enolase. Brain Nerve 67, 967–972.

Iranzo, A., Graus, F., Clover, L., Morera, J., Bruna, J., Vilar, C., Martinez-Rodriguez, J.E., Vincent, A., Santamaria, J., 2006. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. Ann. Neurol. 59, 178–181.

Kikumoto, M., Nagai, M., Ohshita, T., Toko, M., Kato, M., Dote, K., Yamashita, H., 2018. Insular cortex lesion and autonomic instability in a herpes simplex virus encephalitis patient. J. Neuro-Oncol. 24, 649–651.

King, E., O'brien, J.T., Donaghy, P., Morris, C., Barnett, N., Olsen, K., Martin-Ruiz, C., Taylor, J.P., Thomas, A.J., 2018. Peripheral inflammation in prodromal Alzheimer's and Lewy body dementias. J. Neurol. Neurosurg. Psychiatry 89, 339–345.

Mckeith, I., Taylor, J.P., Thomas, A., Donaghy, P., Kane, J., 2016. Revisiting DLB diagnosis: a consideration of prodromal DLB and of the diagnostic overlap with Alzheimer disease. J. Geriatr. Psychiatry Neurol. 29, 249–253.

Mckeith, I.G., Boeve, B.F., Dickson, D.W., Halliday, G., Taylor, J.P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C.G., Bayston, A., Beach, T.G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J.E., El-Agnaf, O., Feldman, H., Ferman, T.J., Ffytche, D., Fujishiro, H., Galasko, D., Goldman, J.G., Gomperts, S.N., Graff-Radford, N.R., Honig, L.S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V.M.Y., Leverenz, J.B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., Mclean, P., Mollenhauer, B., Montine, T.J., Moreno, E., Mori, E., Murray, M., O'brien, J.T., Orimo, S., Postuma, R.B., Ramaswamy, S., Ross, O.A., Salmon, D.P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J.B., Trojanowski, J.Q., Tsuang, D., Walker, Z., Yamada, M., Kosaka, K., 2017. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 89, 88–100.

Mckeon, A., Lennon, V.A., Pittock, S.J., 2010. Immunotherapy-responsive dementias and encephalopathies. Continuum (Minneap Minn) 16, 80–101.

Probasco, J.C., Solnes, L., Nalluri, A., Cohen, J., Jones, K.M., Zan, E., Javadi, M.S., Venkatesan, A., 2018. Decreased occipital lobe metabolism by FDG-PET/CT: an anti-NMDA receptor encephalitis biomarker. Neurol. Neuroimmunol. Neuroinflamm. 5, e413.

Surendranathan, A., Rowe, J.B., O'brien, J.T., 2015. Neuroinflammation in Lewy body dementia. Parkinsonism Relat. Disord. 21, 1398–1406.