Journal of Neurology (2019) 266:2743–2751
https://doi.org/10.1007/s00415-019-09461-3

ORIGINAL COMMUNICATION

Clinical characteristics of autoimmune disorders in the central nervous system associated with myasthenia gravis

Kimitoshi Kimura[1,2,3] · Yoichiro Okada[1,4] · Chihiro Fujii[5] · Kenichi Komatsu[2] · Ryosuke Takahashi[1] · Sadayuki Matsumoto[2] · Takayuki Kondo[2,4]

Received: 11 May 2019 / Revised: 2 July 2019 / Accepted: 8 July 2019 / Published online: 24 July 2019

Abstract

Myasthenia gravis (MG) is occasionally associated with autoimmune diseases in the central nervous system (CNS), such as neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS), Morvan syndrome, and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Here, we report five original cases associated with autoimmune disorders in the CNS among 42 patients with MG in a single tertiary hospital in Japan (11.9%). In four of these five cases, the second disease developed when the preceding disease was unstable. Accurate diagnosis of the newly developing disease may be difficult in such cases, because some neurological symptoms can be seen in both disorders. This implies the great importance of recognizing the possible co-occurrence of MG and disorders in the CNS. In addition, a comprehensive review of the literature revealed distinct clinical characteristics depending on the associated disease in the CNS, including thymic pathology and temporal relationship between MG and associated CNS disorders. Notably, NMOSD usually develops after the onset of MG and thymectomy, in clear contrast to MS. Thymoma is highly prevalent among patients with Morvan syndrome, in contract to cases with NMOSD and MS. The analysis of clinical characteristics, representing the first such investigation to the best of our knowledge, suggests different pathogeneses of these autoimmune diseases in the CNS, and provides significant implications for clinical practice.

Keywords Myasthenia gravis (MG) · Neuromyelitis optica spectrum disorder (NMOSD) · Multiple sclerosis (MS) · Morvan syndrome · Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis

Introduction

Various reports have noted that several autoimmune diseases in the central nervous system (CNS) occasionally coexist with myasthenia gravis (MG), such as neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS), Morvan syndrome, and anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis [1–4]. Although a few case reports have described a high rate of association of MG with some of these autoimmune CNS disorders, the relationship between accompanying CNS disorders and clinical features of MG remains unclear [1, 2, 4]. We present herein a case series of autoimmune diseases in the CNS associated with MG, along with a comprehensive review of the literature. Notably, we found some distinct features, such as MG onset and thymus condition depending on the accompanying CNS disorders.

✉ Takayuki Kondo
takakon78@hotmail.com

1 Department of Neurology , Kyoto University Graduate School of Medicine , 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

2 Department of Neurology , Kitano Hospital, Tazuke Kofukai Medical Research Institute , 2-4-20 Ogimachi, Kita-ku, Osaka 530-8480, Japan

3 Department of Immunology, National Center of Neurology and Psychiatry , National Institute of Neuroscience , 4-1-1 Ogawahigashi, Kodaira 187-8502, Tokyo, Japan

4 Department of Neurology , Kansai Medical University Medical Center , 10-15 Fumizonocho, Moriguchi 570-8507, Osaka, Japan

5 Department of Neurology, Graduate School of Medical Science , Kyoto Prefectural University of Medicine , 465 Kajiicho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

Materials and methods

Patients

Data from patients with MG who visited Kitano Hospital, a tertiary hospital in Japan, from January 2009 to December 2013 were retrospectively reviewed. The diagnosis of MG was based on clinical findings including improvement of symptoms with anticholinesterase, decremental muscle response to a 3-Hz train of repetitive nerve stimuli, or the presence of antibodies against acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK), after exclusion of possible other causes. International consensus diagnostic criteria were used to diagnose NMOSD [5]. Written informed consent was obtained from all the described patients who could be traced, and the study was approved by the institutional review board at Kitano Hospital (P17-11-002).

Review of the literature

Clinical information was obtained from cases with MG and comorbid autoimmune disorders in the CNS that were reported between January 1980 and December 2018. These cases were identified in PubMed, using the terms "myasthenia gravis", "neuromyelitis optica", "multiple sclerosis", "clinically isolated syndrome", "myelitis", "acute disseminated encephalomyelitis", "Morvan syndrome", and "NMDAR encephalitis".

Statistical analysis

Data were analyzed using Prism software (GraphPad Software, CA, USA). One-way analysis of variance (ANOVA) with the Tukey–Kramer comparison test and a Chi square test with Bonferroni test was used, as appropriate. Differences were regarded as significant for values of $p < 0.05$.

Results

Case report

Five cases of MG were associated with autoimmune disorders in the CNS, among 42 cases of MG (11.9%) in a single tertiary hospital.

Case 1: MG preceding NMOSD

A 47-year-old Asian woman presented with ptosis. Anti-AChR antibody was detected and ocular myasthenia gravis was diagnosed. She was treated with steroid and underwent thymectomy the next year. Pathological examination revealed thymic hyperplasia. Five months after thymectomy, she developed myelitis, but anti-aquaporin 4 (AQP4) antibody was not detected. Recurrent myelitis and optic neuritis followed, and treatment with steroid and tacrolimus successfully controlled disease activity. However, a longitudinally extensive thoracic spinal cord lesion developed 4 years later. Cells and protein levels were slightly increased in the cerebrospinal fluid (CSF) (12 cells/μL and 42 mg/dL, respectively). Immunoglobulin (Ig) G index was not elevated (0.55) and no oligoclonal IgG bands were detected. Repeated examination revealed positive results for anti-AQP4 antibody.

Case 2: MG preceding NMOSD

A 48-year-old Asian man presented with ptosis and mild systemic weakness. Anti-AChR antibody was detected and generalized MG was diagnosed. He underwent thymectomy 2 years later, which revealed no abnormality. Worsening of disease was seen three times during the following 11 years. Ten months after the third worsening of MG, bilateral optic neuritis developed despite sustained treatment with steroid and tacrolimus. Four years later, a relapse developed in the pons and the thoracic spinal cord. Anti-AQP4 antibody was detected. Cells and protein levels were not increased in the CSF (1 cell/μL and 33 mg/dL, respectively), and IgG index was not elevated (0.64).

Case 3: NMOSD preceding MG

A 31-year-old Asian woman developed an inflammatory lesion in the pons. Seven months later, a relapse occurred in the cervical spinal cord and interferon (IFN) β was started. When another relapse developed in the midbrain 5 months later, fluctuating ptosis and diplopia were recognized at the same time. Both anti-AChR and anti-AQP4 antibodies were detected, and IFN β was stopped. In addition to two attacks in the thoracic spinal cord in the next year, 2009, another relapse around the third ventricle and concurrent systemic worsening of MG developed in January 2010, despite sustained treatment with steroid and tacrolimus. Ten months later, she underwent thymectomy, which revealed no abnormality. A relapse in the brainstem was identified in 2011, and worsening of MG in the cervical muscles occurred in 2012. Cells and protein levels were not increased in the CSF (3 cell/μL and 31 mg/dL, respectively), and oligoclonal IgG bands were not detected.

Case 4: MG preceding CIS

A 41-year-old Asian man presented with diplopia and dysphagia. Anti-AChR antibody was detected, and generalized MG was diagnosed. He underwent thymectomy in the next year, revealing thymoma. After successful treatment with steroid and tacrolimus for 22 years, he developed an inflammatory lesion in the midbrain. Anti-AQP4 antibody was not detected. Cells and protein levels were slightly increased in the CSF (8 cell/μL and 70 mg/dL, respectively). IgG index was not elevated (0.52), and oligoclonal IgG bands were not detected.

Case 5: MG preceding anti-NMDAR encephalitis

A 74-year-old Asian woman presented with severe systemic weakness and was found to be in myasthenic crisis. Anti-AChR antibody was detected. She was treated with steroid, tacrolimus and thymectomy, which alleviated her symptoms. No abnormality was detected in the resected thymus. Systemic weakness worsened 3 years later and fluctuated during the following 2 years. She then developed disturbance of consciousness. Cells were slightly increased and protein level was within normal limits in the CSF (11 cell/μL and 40 mg/dL, respectively). IgG index was not elevated (0.60), and oligoclonal IgG bands were not detected. MRI showed no characteristic signal changes in the brain. Anti-AQP4 antibody was not detected, but anti-NMDAR antibody was present. Systemic examination detected no tumor.

Clinical characteristics of patients with MG and an autoimmune disorder in the CNS

Previous studies have reported several disorders in the CNS associated with MG, of which NMOSD, MS, and Morvan syndrome comprised the majority [1, 2, 4]. However, the distinct clinical features of MG depending on the associated CNS disorders have not been clarified. The current analysis offers the first descriptions of MG characteristics specific to each associated CNS disorder, to the best of our knowledge (Table 1). This table describes the clinical profiles of cases (including our five cases) showing MG associated with one of the disorders in the CNS: NMOSD, MS, Morvan syndrome, CIS, recurrent myelitis, ADEM, and anti-NMDAR encephalitis. Statistical analyses were performed among cases with NMOSD, MS, and Morvan syndrome. The other disorders listed in Table 1 were excluded from statistical analyses because CIS is a heterogeneous disease entity including an early stage of MS or NMOSD, and because the other associated diseases have been reported in a relatively small number of patients.

Most patients with any associated CNS disorder had early-onset MG, in which the age at onset is less than 50 years. The rate of early-onset MG associated with CNS disorder was apparently higher than the rate reported in the total MG population (35.8–49.7%). Mean age at the onset of MG and CNS disorders was significantly higher in Morvan syndrome compared with NMOSD and MS. The male-to-female ratio was significantly higher in Morvan syndrome than in NMOSD or MS. Most patients associated with any of the three CNS disorders had generalized MG. The positive rate of AChR antibody was significantly lower in MS than in NMOSD or Morvan syndrome. Notably, the rate of thymectomy, histology of resected thymus, and temporal relationship between thymectomy, onset of MG, and onset of associated CNS disorders clearly differed depending on the associated CNS disease. Most patients with Morvan syndrome had thymoma (77.3% of all the patients). Thymoma was reported in only two patients with NMOSD and no patients with MS. The rate of thymectomy was significantly higher in NMOSD and Morvan syndrome than in MS (68.8%, 81.8%, and 25%, respectively). Interestingly, MG predominantly preceded NMOSD (88.9%). In contrast, MS preceded MG in most patients (80.0%). Although the difference in temporal relationship between MG and the associated disorder is partially because the onset of MS is earlier than that of NMOSD in general [6, 7], this cannot explain the difference in onset age of MG between NMOSD and MS groups in the current analysis (mean age 28.1 and 36.6 years, respectively). Furthermore, the characteristic temporal relationship between onset of MG and NMOSD cannot result from random chance, given that age of onset is similar between these diseases (MG: 31.9–56.3 years; NMOSD: 32.6–45.7 years) [6–12]. Notably, NMOSD develops after thymectomy in 64.1% of all the cases, which is in clear contrast to cases with MS (0%).

Discussion

We have shown five patients who developed MG associated with autoimmune disorder involving the CNS. The incidence rate was 11.9% among 42 patients with MG in a single tertiary hospital, which appeared surprisingly high. However, our observations were consistent with a previous report describing signs of CNS involvement in 24 of 164 patients with MG (14.6%), including 15 exhibiting features indicative of NMOSD [13]. Anti-AQP4 antibody was detected in 7 of the 14 patients tested in this study [13]. In the cases with MG and NMOSD, anti-AChR and anti-AQP4 antibody titers were reported to change in opposing directions [1]. MG was usually mild at the onset of NMOSD, and MG relapse was rare once NMOSD developed [1]. However, this

Table 1 Clinical characteristics of cases with concurrent MG and autoimmune or inflammatory disorders in the CNS

	NMOSD[A] [1–3, 39–62]	MS [2, 63–70]	Morvan syndrome [4, 71–81]	CIS [3, 46, 82]	Recurrent myelitis [3, 83]	ADEM [3]	Anti-NMDAR encephalitis [39]	General clinical characteristics of MG [8–12, 84]	*p* value
n	65[B]	20	22	6	2	1	2[B]	122–1152	NA
M:F (female %)	5:56 (91.8%) (*n* = 61)	3:17 (85%) (*n* = 20)	10:2 (28.6%) (*n* = 13)	3:3 (50%) (*n* = 6)	1:0 (0%) (*n* = 1)	0:1 (100%) (*n* = 1)	0:2 (100%) (*n* = 2)	50.4–69.7%	< 0.0001 (b, c)
Mean age at the onset of MG	28.1 (8–56) (*n* = 58)	36.6 (16–53) (*n* = 20)	48.6 (39–70) (*n* = 8)	28.0 (14–41) (*n* = 6)	23.5 (23–24) (*n* = 2)	71 (*n* = 1)	49 (24–74) (*n* = 2)	31.9–56.3	< 0.0001 (a, b, c)
Mean age at the onset of CNS disorders	40.6 (14–70) (*n* = 60)	30.8 (18–51) (*n* = 20)	51.0 (39–76) (*n* = 8)	46.2 (23–81) (*n* = 6)	41 (41–41) (*n* = 2)	73 (*n* = 1)	58 (37–79) (*n* = 2)	NA	0.0006 (a, c)
MG clinical type (ocular: generalized) (ocular %)	9:42 (17.6%) (*n* = 51)	1:7 (12.5%) (*n* = 8)	1:11 (8.3%) (*n* = 12)	1:5 (16.7%) (*n* = 6)	0:2 (0%) (*n* = 2)	0:1 (0%) (*n* = 1)	0:1 (0%) (*n* = 1)	5.1–25.2%	n.s
Early-onset MG	57 (96.6%) (*n* = 59)	17 (85%) (*n* = 20)	8 (80%) (*n* = 10)	6 (100%) (*n* = 6)	2 (100%) (*n* = 2)	0 (0%) (*n* = 1)	1 (50%) (*n* = 2)	35.8–49.7%	n.s
AChR-Ab	56 (96.6%) (*n* = 58)[C]	8 (42.1%) (*n* = 19)[C]	16 (100%) (*n* = 16)[D]	4 (100%) (*n* = 4)	2 (100%) (*n* = 2)	1 (100%) (*n* = 1)	2 (100%) (*n* = 2)	73.2–83.6%	< 0.0001 (a, c)
AQP4-Ab	46 (85.2%) (*n* = 54)	NA	NA	0 (0%) (*n* = 1)	NA	NA	1 (50%) (*n* = 2)	NA	NA
VGKC-Ab	NA	NA	20 (95.2%) (*n* = 21)[E]	NA	NA	NA	NA	NA	NA
NMDAR-Ab	NA	NA	NA	NA	NA	NA	2 (100%) (*n* = 2)	NA	NA
Thymectomy	44 (68.8%) (*n* = 64)	5 (25%) (*n* = 20)	18 (81.8%) (*n* = 22)	4 (66.7%) (*n* = 6)	2 (100%) (*n* = 2)	0 (0%) (*n* = 1)	2 (100%) (*n* = 2)	27.5–72.2%	0.0002 (a, c)
Histology of thymus (/resected cases)									
Thymic hyperplasia (/resected cases)	25 (67.6%) (*n* = 37)	4 (100%) (*n* = 4)	0 (0%) (*n* = 17)	2 (66.7%) (*n* = 3)	1 (100%) (*n* = 1)	NA	0 (0%) (*n* = 1)	NA	NA
Thymic hyperplasia (/all the cases)	25 (38.5%) (*n* = 65)	4 (20%) (*n* = 20)	0 (0%) (*n* = 22)	2 (33.3%) (*n* = 6)	1 (50%) (*n* = 2)	NA	0 (0%) (*n* = 2)	19.1–30.3%	0.0016 (b)
Thymoma (/resected cases)	2 (5.4%) (*n* = 37)	0 (0%) (*n* = 4)	17 (100%) (*n* = 17)	1 (33.3%) (*n* = 3)	0 (0%) (*n* = 1)	NA	0 (0%) (*n* = 1)	NA	NA
Thymoma (/all the cases)	2 (3.1%) (*n* = 65)	0 (0%) (*n* = 20)	17 (77.3%) (*n* = 22)	1 (16.7%) (*n* = 6)	0 (0%) (*n* = 2)	NA	0 (0%) (*n* = 2)	6.9–18.5%	< 0.0001 (b, c)
No abnormality (/resected cases)	8 (21.6%) (*n* = 37)	0 (0%) (*n* = 4)	0 (0%) (*n* = 17)	0 (0%) (*n* = 3)	0 (0%) (*n* = 1)	NA	1 (100%) (*n* = 1)	NA	NA
Thymectomy preceding CNS disorders	41 (64.1%) (*n* = 64)	0 (0%) (*n* = 18)[F]	6 (54.5%) (*n* = 11)[G]	3 (50%) (*n* = 6)	2 (100%) (*n* = 2)	0 (0%) (*n* = 1)	2 (100%) (*n* = 2)	NA	< 0.0001 (a, c)
Disease course									
MG preceding CNS disorders	56 (88.9%) (*n* = 63)	4 (20%) (*n* = 20)	7 (63.6%) (*n* = 11)	5 (83.3%) (*n* = 6)	2 (100%) (*n* = 2)	1 (100%) (*n* = 1)	2 (100%) (*n* = 2)	NA	< 0.0001 (a)

Table 1 (continued)

	NMOSD[A] [1–3, 39–62]	MS [2, 63–70]	Morvan syndrome [4, 71–81]	CIS [3, 46, 82]	Recurrent myelitis [3, 83]	ADEM [3]	Anti-NMDAR encephalitis [39]	General clinical characteristics of MG [8–12, 84]	*p* value
CNS disorders preceding MG	6 (9.5%) ($n=63$)	16 (80%) ($n=20$)	0 (0%) ($n=11$)	1 (16.7%) ($n=6$)	0 (0%) ($n=2$)	0 (0%) ($n=1$)	0 (0%) ($n=2$)	NA	<0.0001 (a, c)
Same onset suspected	1 (1.6%) ($n=63$)	0 (0%) ($n=20$)	4 (36.4%) ($n=11$)	0 (0%) ($n=6$)	0 (0%) ($n=2$)	0 (0%) ($n=1$)	0 (0%) ($n=2$)	NA	<0.0001 (b, c)

A one-way ANOVA with Turkey–Kramer comparison test and a Chi square test with Bonferroni test were used. a: significant difference between NMOSD and MS; b: between NMOSD and Morvan syndrome; c: between MS and Morvan syndrome

[A]This category includes both definite and suspected NMOSD cases that have a characteristic manifestation such as concurrent bilateral optic neuritis and transverse myelitis

[B]One patient with MG, NMOSD, and anti-NMDAR encephalitis is included

[C]Anti-MuSK antibody was positive in one patient without anti-AChR antibody

[D]One patient had both anti-AChR and anti-MuSK antibodies

[E]Anti-CASPR2 antibody was detected in 16 out of 17 patients examined, and anti-LGI1 antibody was detected in 6 out of 10 patients examined. All of the latter 6 patients had also anti-CASPR2 antibody

[F]Out of 5 cases with thymectomy, the temporary relationship with the onset of CNS disorders was not available in 2 cases

[G]Out of 18 cases with thymectomy, the temporary relationship with the onset of CNS disorders was not available in 11 cases. Morvan syndrome occurred with recurrence of thymoma in one case with thymectomy preceding Morvan syndrome

is not necessarily true. NMOSD could develop soon after resolution of the last exacerbation of MG, as in our cases 1 and 2. Moreover, attacks of MG and NMOSD could occur simultaneously as in our case 3. When neurological deficit is noticed in the clinical course of either disease, the possibility of a concomitant disease should be recognized even when the activity of the preceding disease is high.

This is the first study to analyze temporal associations and thymic condition of MG between various associated autoimmune disorders in the CNS. The clear differences depending on the CNS disorder might reflect different disease pathogeneses. Among the three most prevalent diseases in the CNS associated with MG (NMOSD, MS, and Morvan syndrome), Morvan syndrome was characterized by a pronounced relationship with thymoma. This might explain the significantly later onset of MG associated with Morvan syndrome (Table 1), because thymoma-associated MG frequently occur after 50 years of age [14]. Thymoma was diagnosed in 77.3% of all the patients with Morvan syndrome. In addition, some of the other cases with Morvan syndrome might have small thymomas that were difficult to detect. Besides the general pathogenesis of paraneoplastic syndrome, where ectopic antigen presentation in the tumor induces an immunological attack on normal relevant tissues, thymoma shows a unique mechanism in the development of autoimmunity. Autoimmune regulator (AIRE) is critically involved in both the expression of self-antigens within the thymus and induction of tolerance [15]. Defective expression of AIRE and major histocompatibility complex (MHC) class II is a characteristic feature of thymoma, and leads to insufficient negative selection and subsequent survival of autoreactive T cells, including those targeting AChR [14, 16]. Furthermore, defective expression of AIRE is also associated with deficiency of regulatory T (Treg) cells [14, 17, 18]. These factors result in a high frequency of autoimmune diseases, including MG and Morvan syndrome, associated with thymoma ($>50\%$) compared with tumors of other organs ($<5\%$) [19, 20]. A previous report suggested that T cells exported from thymoma can persist in the periphery for many years after thymectomy [21]. This might partially explain the development of Morvan syndrome after resection of thymoma in some cases (Table 1).

One previous study reported that the prevalence of MG is not increased among cases with MS [22]. Therefore, association of MS and MG could be a mere coincidence. This may be because MS is rather a T cell-mediated disease and different from antibody-mediated disorders such as MG, NMOSD, and Morvan syndrome. Some of the cases with MS in the previous reports might have been NMOSD or myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease, before anti-AQP4 and -MOG antibodies were discovered to be probably pathogenic. However,

differences between MG cases comorbid with NMOSD and MS were still apparent (Table 1). Notably, MG and thymectomy preceded onset of NMOSD in most cases, whereas MS did not follow thymectomy. The resected thymuses in cases with NMOSD were shown to be mainly hyperplastic. Thymic hyperplasia is characterized by the formation of germinal centers containing a large number of B cells, where hypermutation of B cell receptor genes and production of high-affinity autoantibodies, including anti-AChR antibody, are accelerated [14, 23]. Treg cells were also disclosed to be functionally impaired in the hyperplastic thymus [24]. These findings explain the clinical benefit of thymectomy in MG [14]. However, NMOSD comorbid with MG frequently develops after thymectomy, even though anti-AQP4 antibody is detected prior to thymectomy without any relevant symptoms in some such cases [1]. The main subclass of anti-AQP4 antibody is IgG1, the same as anti-AChR antibody in MG. A difference between MG and NMOSD that might be involved in this discrepancy is the fact that AQP4 is absent or expressed at low levels in normal thymus, in contrast to constantly expressed AChR [25, 26]. Thymectomy is also generally recognized to induce production of autoantibodies and development of systemic autoimmune diseases [27]. The difference in pathogenesis between diseases that precede and follow thymectomy warrants further investigation.

No characteristics regarding pathology of the thymus or thymectomy were apparent in patients with MS. Disease-modifying drugs are one possible cause of MG among cases with preceding CNS disorders, especially MS. In 5 of the 16 patients with MS preceding MG, IFNβ was started before the onset of MG, with an interval ranging from 11 days to 3 years. In another patient, initiation of IFNβ after the onset of MG exacerbated myasthenic symptoms. One patient was receiving glatiramer acetate and one was receiving alemtuzumab at the onset of MG. In addition, two patients were treated with IFNβ at the onset of MG among six patients with NMOSD preceding MG. IFNβ treatment was shown to increase levels of several autoantibodies among patients with MS [28] and IFNβ administration for the treatment of hepatitis C reportedly exacerbated myasthenia gravis [29]. Glatiramer acetate is known to shift the balance of helper T cells from Th1 to Th2, which might be involved in the development of antibody-mediated autoimmunity [30].

It is well appreciated that human leukocyte antigen (HLA) is implicated in various autoimmune diseases as a major susceptibility gene [31]. HLA-DRB1*16 allele was reported to be associated with anti-AChR antibody-positive MG in Italy [32], and HLA-DRB1*16:02 is known to be a risk allele of anti-AQP4 antibody-positive NMOSD in Japan [33]. Moreover, HLA-DRB1*15:01 was suggested to be a risk allele for both diseases [34, 35]. These results indicate the same risk allele, although there are no known definite ones shared between MG and Morvan syndrome. Several previous studies identified different HLA risk alleles of MG depending on ethnicity and disease type, such as early-onset and late-onset MG [36]. The same is true for NMOSD and diseases caused by anti-voltage-gated potassium-channel (VGKC) antibody [37, 38]. Therefore, comorbidity of MG with NMOSD or other autoimmune CNS disorders might be associated with the presence of some unrevealed specific susceptibility alleles. MG cases with autoimmune CNS disorders should be separated as a distinct disease group, to identify such risk alleles. This is still an open question that should be clarified in future. Revealing such background might contribute to more fundamental understanding of these associated disorders.

It should be noted that one limitation of this study is the relatively small sample size in a single tertiary hospital. Further prospective multi-center studies are warranted to precisely evaluate the incidence of autoimmune CNS disorders among patients with MG.

Conclusion

MG is occasionally associated with various autoimmune diseases in the CNS. As the association is more prevalent than previously expected, neurologists should recognize the possibility in clinical practice that hidden autoimmune CNS disorders may be present among patients with MG irrespective of disease activity, and vice versa. In addition, the distinct clinical characteristics depending on the associated CNS disorders suggest different disease pathogeneses.

Acknowledgements We acknowledge Toshiyuki Takahashi (Department of Neurology, Tohoku University Graduate School of Medicine) as a contributor for detection of anti-AQP4 antibody.

Author contributions KK contributed study concept and design; acquisition, analysis, and interpretation of data; and drafting and revising the manuscript for intellectual content. YO contributed revising the manuscript for intellectual content. CF contributed revising the manuscript for intellectual content. KK contributed acquisition of data, and revising the manuscript for intellectual content. RT contributed revising the manuscript for intellectual content. SM contributed revising the manuscript for intellectual content. TK contributed study concept and design, analysis, and interpretation of data, drafting and revising the manuscript for intellectual content.

Compliance with ethical standards

Conflicts of interest On behalf of all the authors, the corresponding author states that there is no conflict of interest.

Ethical standards All studies in this review have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Leite MI, Coutinho E, Lana-Peixoto M, Apostolos S, Waters P, Sato D, Melamud L, Marta M, Graham A, Spillane J, Villa AM, Callegaro D, Santos E, da Silva AM, Jarius S, Howard R, Nakashima I, Giovannoni G, Buckley C, Hilton-Jones D, Vincent A, Palace J (2012) Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. Neurology 78(20):1601–1607. https://doi.org/10.1212/WNL.0b013e31825644ff
2. Isbister CM, Mackenzie PJ, Anderson D, Wade NK, Oger J (2003) Co-occurrence of multiple sclerosis and myasthenia gravis in British Columbia. Mult Scler 9(6):550–553. https://doi.org/10.1191/1352458503ms964oa
3. Gotkine M, Fellig Y, Abramsky O (2006) Occurrence of CNS demyelinating disease in patients with myasthenia gravis. Neurology 67(5):881–883. https://doi.org/10.1212/01.wnl.0000234142.41728.a0
4. Irani SR, Pettingill P, Kleopa KA, Schiza N, Waters P, Mazia C, Zuliani L, Watanabe O, Lang B, Buckley C, Vincent A (2012) Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol 72(2):241–255. https://doi.org/10.1002/ana.23577
5. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, de Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lana-Peixoto M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Wellik KE, Weinshenker BG (2015) International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85(2):177–189. https://doi.org/10.1212/WNL.0000000000001729
6. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG (2007) The spectrum of neuromyelitis optica. Lancet Neurol 6(9):805–815. https://doi.org/10.1016/s1474-4422(07)70216-8
7. Pandit L, Asgari N, Apiwattanakul M, Palace J, Paul F, Leite MI, Kleiter I, Chitnis T (2015) Demographic and clinical features of neuromyelitis optica: a review. Mult Scler 21(7):845–853. https://doi.org/10.1177/1352458515572406
8. Murai H, Masuda M, Utsugisawa K, Nagane Y, Suzuki S, Imai T, Motomura M, Konno S, Kira J-i (2014) Clinical features and treatment status of adult myasthenia gravis in Japan. Clin Exp Neuroimmunol 5(1):84–91. https://doi.org/10.1111/cen3.12091
9. Blum S, Lee D, Gillis D, McEniery DF, Reddel S, McCombe P (2015) Clinical features and impact of myasthenia gravis disease in Australian patients. J Clin Neurosci 22(7):1164–1169. https://doi.org/10.1016/j.jocn.2015.01.022
10. Aguiar Ade A, Carvalho AF, Costa CM, Fernandes JM, D'Almeida JA, Furtado LE, Cunha FM (2010) Myasthenia gravis in Ceara, Brazil: clinical and epidemiological aspects. Arq Neuropsiquiatr 68(6):843–848
11. Karni A, Asmail A, Drory VE, Kolb H, Kesler A (2016) Thymus involvement in myasthenia gravis: epidemiological and clinical impacts of different self-tolerance breakdown mechanisms. J Neuroimmunol 298:58–62. https://doi.org/10.1016/j.jneuroim.2016.07.002
12. Mantegazza R, Beghi E, Pareyson D, Antozzi C, Peluchetti D, Sghirlanzoni A, Cosi V, Lombardi M, Piccolo G, Tonali P et al (1990) A multicentre follow-up study of 1152 patients with myasthenia gravis in Italy. J Neurol 237(6):339–344
13. Vaknin-Dembinsky A, Abramsky O, Petrou P, Ben-Hur T, Gotkine M, Brill L, Brenner T, Argov Z, Karussis D (2011) Myasthenia gravis-associated neuromyelitis optica-like disease: an immunological link between the central nervous system and muscle? Arch Neurol 68(12):1557–1561. https://doi.org/10.1001/archneurol.2011.200
14. Marx A, Pfister F, Schalke B, Saruhan-Direskeneli G, Melms A, Strobel P (2013) The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev 12(9):875–884. https://doi.org/10.1016/j.autrev.2013.03.007
15. Kyewski B, Peterson P (2010) Aire, master of many trades. Cell 140(1):24–26. https://doi.org/10.1016/j.cell.2009.12.036
16. Strobel P, Murumagi A, Klein R, Luster M, Lahti M, Krohn K, Schalke B, Nix W, Gold R, Rieckmann P, Toyka K, Burek C, Rosenwald A, Muller-Hermelink HK, Pujoll-Borrell R, Meager A, Willcox N, Peterson P, Marx A (2007) Deficiency of the autoimmune regulator AIRE in thymomas is insufficient to elicit autoimmune polyendocrinopathy syndrome type 1 (APS-1). J Pathol 211(5):563–571. https://doi.org/10.1002/path.2141
17. Strobel P, Rosenwald A, Beyersdorf N, Kerkau T, Elert O, Murumagi A, Sillanpaa N, Peterson P, Hummel V, Rieckmann P, Burek C, Schalke B, Nix W, Kiefer R, Muller-Hermelink HK, Marx A (2004) Selective loss of regulatory T cells in thymomas. Ann Neurol 56(6):901–904. https://doi.org/10.1002/ana.20340
18. Scarpino S, Di Napoli A, Stoppacciaro A, Antonelli M, Pilozzi E, Chiarle R, Palestro G, Marino M, Facciolo F, Rendina EA, Webster KE, Kinkel SA, Scott HS, Ruco L (2007) Expression of autoimmune regulator gene (AIRE) and T regulatory cells in human thymomas. Clin Exp Immunol 149(3):504–512. https://doi.org/10.1111/j.1365-2249.2007.03442.x
19. Marx A, Willcox N, Leite MI, Chuang WY, Schalke B, Nix W, Strobel P (2010) Thymoma and paraneoplastic myasthenia gravis. Autoimmunity 43(5–6):413–427. https://doi.org/10.3109/08916930903555935
20. Holbro A, Jauch A, Lardinois D, Tzankov A, Dirnhofer S, Hess C (2012) High prevalence of infections and autoimmunity in patients with thymoma. Hum Immunol 73(3):287–290. https://doi.org/10.1016/j.humimm.2011.12.022
21. Buckley C, Douek D, Newsom-Davis J, Vincent A, Willcox N (2001) Mature, long-lived CD4+ and CD8+ T cells are generated by the thymoma in myasthenia gravis. Ann Neurol 50(1):64–72
22. Ramagopalan SV, Dyment DA, Valdar W, Herrera BM, Criscuoli M, Yee IM, Sadovnick AD, Ebers GC (2007) Autoimmune disease in families with multiple sclerosis: a population-based study. Lancet Neurol 6(7):604–610. https://doi.org/10.1016/S1474-4422(07)70132-1
23. Berrih-Aknin S, Le Panse R (2014) Myasthenia gravis: a comprehensive review of immune dysregulation and etiological mechanisms. J Autoimmun 52:90–100. https://doi.org/10.1016/j.jaut.2013.12.011
24. Balandina A, Lecart S, Dartevelle P, Saoudi A, Berrih-Aknin S (2005) Functional defect of regulatory CD4(+)CD25+ T cells in the thymus of patients with autoimmune myasthenia gravis. Blood 105(2):735–741. https://doi.org/10.1182/blood-2003-11-3900
25. Chan KH, Kwan JS, Ho PW, Ho SL, Chui WH, Chu AC, Ho JW, Zhang WY, Kung MH (2010) Aquaporin-4 water channel expression by thymoma of patients with and without myasthenia gravis. J Neuroimmunol 227(1–2):178–184. https://doi.org/10.1016/j.jneuroim.2010.07.016
26. Handel AE, Irani SR, Hollander GA (2018) The role of thymic tolerance in CNS autoimmune disease. Nat Rev Neurol 14(12):723–734. https://doi.org/10.1038/s41582-018-0095-7
27. Gerli R, Paganelli R, Cossarizza A, Muscat C, Piccolo G, Barbieri D, Mariotti S, Monti D, Bistoni O, Raiola E, Venanzi FM, Bertotto A, Franceschi C (1999) Long-term immunologic effects of thymectomy in patients with myasthenia gravis. J Allergy Clin Immunol 103(5 Pt 1):865–872
28. Speciale L, Saresella M, Caputo D, Ruzzante S, Mancuso R, Calvo MG, Guerini FR, Ferrante P (2000) Serum auto antibodies presence in multiple sclerosis patients treated with beta-interferon 1a and 1b. J Neurovirol 6(Suppl 2):S57–61

29. Harada H, Tamaoka A, Kohno Y, Mochizuki A, Shoji S (1999) Exacerbation of myasthenia gravis in a patient after interferon-beta treatment for chronic active hepatitis C. J Neurol Sci 165(2):182–183
30. Miller A, Shapiro S, Gershtein R, Kinarty A, Rawashdeh H, Honigman S, Lahat N (1998) Treatment of multiple sclerosis with copolymer-1 (Copaxone): implicating mechanisms of Th1 to Th2/Th3 immune-deviation. J Neuroimmunol 92(1–2):113–121
31. Cho JH, Gregersen PK (2011) Genomics and the multifactorial nature of human autoimmune disease. N Engl J Med 365(17):1612–1623. https://doi.org/10.1056/NEJMra1100030
32. Testi M, Terracciano C, Guagnano A, Testa G, Marfia GA, Pompeo E, Andreani M, Massa R (2012) Association of HLA-DQB1*05:02 and DRB1*16 Alleles with Late-Onset, Nonthymomatous, AChR-Ab-Positive Myasthenia Gravis. Autoimmune Dis 2012:541760. https://doi.org/10.1155/2012/541760
33. Yoshimura S, Isobe N, Matsushita T, Yonekawa T, Masaki K, Sato S, Kawano Y, Kira J (2013) Distinct genetic and infectious profiles in Japanese neuromyelitis optica patients according to anti-aquaporin 4 antibody status. J Neurol Neurosurg Psychiatry 84(1):29–34. https://doi.org/10.1136/jnnp-2012-302925
34. Estrada K, Whelan CW, Zhao F, Bronson P, Handsaker RE, Sun C, Carulli JP, Harris T, Ransohoff RM, McCarroll SA, Day-Williams AG, Greenberg BM, MacArthur DG (2018) A whole-genome sequence study identifies genetic risk factors for neuromyelitis optica. Nature Commun 9(1):1929. https://doi.org/10.1038/s41467-018-04332-3
35. Maniaol AH, Elsais A, Lorentzen AR, Owe JF, Viken MK, Saether H, Flam ST, Brathen G, Kampman MT, Midgard R, Christensen M, Rognerud A, Kerty E, Gilhus NE, Tallaksen CM, Lie BA, Harbo HF (2012) Late onset myasthenia gravis is associated with HLA DRB1*15:01 in the Norwegian population. PLoS ONE 7(5):e36603. https://doi.org/10.1371/journal.pone.0036603
36. Gilhus NE, Verschuuren JJ (2015) Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 14(10):1023–1036. https://doi.org/10.1016/S1474-4422(15)00145-3
37. Papadopoulos MC, Verkman AS (2012) Aquaporin 4 and neuromyelitis optica. Lancet Neurol 11(6):535–544. https://doi.org/10.1016/S1474-4422(12)70133-3
38. Binks S, Varley J, Lee W, Makuch M, Elliott K, Gelfand JM, Jacob S, Leite MI, Maddison P, Chen M, Geschwind MD, Grant E, Sen A, Waters P, McCormack M, Cavalleri GL, Barnardo M, Knight JC, Irani SR (2018) Distinct HLA associations of LGI1 and CASPR2-antibody diseases. Brain 141(8):2263–2271. https://doi.org/10.1093/brain/awy109
39. Titulaer MJ, Hoftberger 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 (2014) Overlapping demyelinating syndromes and anti-*N*-methyl-D-aspartate receptor encephalitis. Ann Neurol 75(3):411–428. https://doi.org/10.1002/ana.24117
40. Goldman M, Herode A, Borenstein S, Zanen A (1984) Optic neuritis, transverse myelitis, and anti-DNA antibodies nine years after thymectomy for myasthenia gravis. Arthritis Rheum 27(6):701–703
41. Lo R, Feasby TE (1983) Multiple sclerosis and autoimmune diseases. Neurology 33(1):97–98
42. Shakir RA, Hussien JM, Trontelj JV (1983) Myasthenia gravis and multiple sclerosis. J Neuroimmunol 4(3):161–165
43. Balarabe SA, Adamu MD, Watila MM, Jiya N (2015) Neuromyelitis optica and myasthenia gravis in a young Nigerian girl. BMJ Case Rep. https://doi.org/10.1136/bcr-2014-207362
44. McKeon A, Lennon VA, Jacob A, Matiello M, Lucchinetti CF, Kale N, Chan KH, Weinshenker BG, Apiwattinakul M, Wingerchuk DM, Pittock SJ (2009) Coexistence of myasthenia gravis and serological markers of neurological autoimmunity in neuromyelitis optica. Muscle Nerve 39(1):87–90. https://doi.org/10.1002/mus.21197
45. Yau GS, Lee JW, Chan TT, Yuen CY (2014) Neuromyelitis optica spectrum disorder in a Chinese woman with ocular myasthenia gravis: first reported case in the Chinese population. Neuroophthalmology 38(3):140–144. https://doi.org/10.3109/01658107.2013.879903
46. Bichuetti DB, Barros TM, Oliveira EM, Annes M, Gabbai AA (2008) Demyelinating disease in patients with myasthenia gravis. Arq Neuropsiquiatr 66(1):5–7
47. Ogaki K, Hirayama T, Chijiiwa K, Fukae J, Furuya T, Noda K, Fujishima K, Hattori N, Takahashi T, Okuma Y (2012) Anti-aquaporin-4 antibody-positive definite neuromyelitis optica in a patient with thymectomy for myasthenia gravis. Neurologist 18(2):76–79. https://doi.org/10.1097/NRL.0b013e318247bc91
48. Uzawa A, Mori M, Iwai Y, Kobayashi M, Hayakawa S, Kawaguchi N, Kuwabara S (2009) Association of anti-aquaporin-4 antibody-positive neuromyelitis optica with myasthenia gravis. J Neurol Sci 287(1–2):105–107. https://doi.org/10.1016/j.jns.2009.08.040
49. Antoine JC, Camdessanche JP, Absi L, Lassabliere F, Feasson L (2004) Devic disease and thymoma with anti-central nervous system and antithymus antibodies. Neurology 62(6):978–980
50. O'Riordan JI, Gallagher HL, Thompson AJ, Howard RS, Kingsley DP, Thompson EJ, McDonald WI, Miller DH (1996) Clinical, CSF, and MRI findings in Devic's neuromyelitis optica. J Neurol Neurosurg Psychiatry 60(4):382–387
51. Kohsaka M, Tanaka M, Tahara M, Araki Y, Mori S, Konishi T (2010) A case of subacute myelitis with anti-aquaporin 4 antibody after thymectomy for myasthenia gravis: review of autoimmune diseases after thymectomy. Rinsho Shinkeigaku 50(2):111–113
52. Jarius S, Paul F, Franciotta D, de Seze J, Munch C, Salvetti M, Ruprecht K, Liebetrau M, Wandinger KP, Akman-Demir G, Melms A, Kristoferitsch W, Wildemann B (2012) Neuromyelitis optica spectrum disorders in patients with myasthenia gravis: ten new aquaporin-4 antibody positive cases and a review of the literature. Mult Scler 18(8):1135–1143. https://doi.org/10.1177/1352458511431728
53. Etemadifar M, Abtahi SH, Dehghani A, Abtahi MA, Akbari M, Tabrizi N, Goodarzi T (2011) Myasthenia gravis during the course of neuromyelitis optica. Case Rep Neurol 3(3):268–273. https://doi.org/10.1159/000334128
54. Furukawa Y, Yoshikawa H, Yachie A, Yamada M (2006) Neuromyelitis optica associated with myasthenia gravis: characteristic phenotype in Japanese population. Eur J Neurol 13(6):655–658. https://doi.org/10.1111/j.1468-1331.2006.01392.x
55. Kister I, Gulati S, Boz C, Bergamaschi R, Piccolo G, Oger J, Swerdlow ML (2006) Neuromyelitis optica in patients with myasthenia gravis who underwent thymectomy. Arch Neurol 63(6):851–856. https://doi.org/10.1001/archneur.63.6.851
56. Kay CS, Scola RH, Lorenzoni PJ, Jarius S, Arruda WO, Werneck LC (2008) NMO-IgG positive neuromyelitis optica in a patient with myasthenia gravis but no thymectomy. J Neurol Sci 275(1–2):148–150. https://doi.org/10.1016/j.jns.2008.06.038
57. Ikeda K, Araki Y, Iwasaki Y (2007) Occurrence of CNS demyelinating disease in patients with myasthenia gravis. Neurology 68(16):1326 **(author reply 1327)**
58. Hironishi M, Ishimoto S, Sawanishi T, Miwa H, Kawachi I, Kondo T (2012) Neuromyelitis optica following thymectomy with severe spinal cord atrophy after frequent relapses for 30 years. Brain Nerve 64(8):951–955
59. Tsujii T, Nishikawa N, Tanabe N, Iwaki H, Nagai M, Nomoto M (2012) Myasthenia gravis complicated with optic neuritis showing

anti-aquaporin 4 antibody: a case report. Rinsho Shinkeigaku 52(7):503–506
60. Ikeguchi R, Shimizu Y, Suzuki S, Shimizu S, Kabasawa C, Hashimoto S, Masuda M, Nagane Y, Utsugisawa K, Suzuki Y, Takahashi T, Utsumi H, Fujihara K, Suzuki N, Uchiyama S (2014) Japanese cases of neuromyelitis optica spectrum disorder associated with myasthenia gravis and a review of the literature. Clin Neurol Neurosurg 125:217–221. https://doi.org/10.1016/j.clineuro.2014.07.036
61. Tola MR, Casetta I, Granieri E, Caniatti LM, Monetti VC, Pascarella R (1996) Systemic lupus erythematosus related recurrent transverse myelitis in a patient with myasthenia gravis and multiple sclerosis. Eur Neurol 36(5):327–328
62. Bibic VC, Brust TB, Burton JM (2018) Neuromyelitis optica spectrum disorder presenting with concurrent autoimmune diseases. Mult Scler Relat Disord 28:125–128. https://doi.org/10.1016/j.msard.2018.12.028
63. Basiri K, Etemadifar M, Maghzi AH, Zarghami N (2009) Frequency of myasthenia gravis in multiple sclerosis: report of five cases from Isfahan, Iran. Neurol India 57(5):638–640. https://doi.org/10.4103/0028-3886.57817
64. Gharagozli K, Shojaei M, Harandi AA, Akbari N, Ilkhani M (2011) Myasthenia gravis development and crisis subsequent to multiple sclerosis. Case Rep Med 2011:291731. https://doi.org/10.1155/2011/291731
65. Dionisiotis J, Zoukos Y, Thomaides T (2004) Development of myasthenia gravis in two patients with multiple sclerosis following interferon beta treatment. J Neurol Neurosurg Psychiatry 75(7):1079
66. Frese A, Bethke F, Ludemann P, Stogbauer F (2000) Development of myasthenia gravis in a patient with multiple sclerosis during treatment with glatiramer acetate. J Neurol 247(9):713
67. Blake G, Murphy S (1997) Onset of myasthenia gravis in a patient with multiple sclerosis during interferon-1b treatment. Neurology 49(6):1747–1748
68. Bixenman WW, Buchsbaum HW (1988) Multiple sclerosis, euthyroid restrictive Grave's ophthalmopathy, and myasthenia gravis. A case report. Graefe's Arch Clin Exp Ophthalmol 226(2):168–171
69. Sylvester J, Purdie G, Slee M, Gray JX, Burnet S, Koblar S (2013) Muscle-specific kinase antibody positive myaesthenia gravis and multiple sclerosis co-presentation: a case report and literature review. J Neuroimmunol 264(1–2):130–133. https://doi.org/10.1016/j.jneuroim.2013.08.016
70. Midaglia L, Gratacos M, Caronna E, Raguer N, Sastre-Garriga J, Montalban X, Tintore M (2018) Myasthenia gravis following alemtuzumab therapy for multiple sclerosis. Neurology 91(13):622–624. https://doi.org/10.1212/WNL.0000000000006251
71. Somer H, Muller K, Kinnunen E (1989) Myasthenia gravis associated with multiple sclerosis. Epidemiological survey and immunological findings. J Neurol Sci 89(1):37–48
72. Lindsey JW, Albers GW, Steinman L (1992) Recurrent transverse myelitis, myasthenia gravis, and autoantibodies. Ann Neurol 32(3):407–409. https://doi.org/10.1002/ana.410320319
73. Mantegazza R, Baggi F, Antozzi C, Confalonieri P, Morandi L, Bernasconi P, Andreetta F, Simoncini O, Campanella A, Beghi E, Cornelio F (2003) Myasthenia gravis (MG): epidemiological data and prognostic factors. Ann N Y Acad Sci 998:413–423
74. Koge J, Hayashi S, Murai H, Yokoyama J, Mizuno Y, Uehara T, Ueda N, Watanabe O, Takashima H, Kira J (2016) Morvan's syndrome and myasthenia gravis related to familial Mediterranean fever gene mutations. J Neuroinflammation 13(1):68. https://doi.org/10.1186/s12974-016-0533-7
75. Briani C, Cagnin A, Blandamura S, Altavilla G (2010) Multiple paraneoplastic diseases occurring in the same patient after thymomectomy. J Neurooncol 99(2):287–288. https://doi.org/10.1007/s11060-010-0130-z
76. Rinaldi C, Russo CV, Filla A, De Michele G, Marano E (2009) Course and outcome of a voltage-gated potassium channel antibody negative Morvan's syndrome. Neurol Sci 30(3):237–239. https://doi.org/10.1007/s10072-009-0041-y
77. Diaz-Manera J, Rojas-Garcia R, Gallardo E, Juarez C, Martinez-Domeno A, Martinez-Ramirez S, Dalmau J, Blesa R, Illa I (2007) Antibodies to AChR, MuSK and VGKC in a patient with myasthenia gravis and Morvan's syndrome. Nat Clin Pract Neurol 3(7):405–410. https://doi.org/10.1038/ncpneuro0526
78. Lancaster E, Huijbers MG, Bar V, Boronat A, Wong A, Martinez-Hernandez E, Wilson C, Jacobs D, Lai M, Walker RW, Graus F, Bataller L, Illa I, Markx S, Strauss KA, Peles E, Scherer SS, Dalmau J (2011) Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol 69(2):303–311. https://doi.org/10.1002/ana.22297
79. Sadnicka A, Reilly MM, Mummery C, Brandner S, Hirsch N, Lunn MP (2011) Rituximab in the treatment of three coexistent neurological autoimmune diseases: chronic inflammatory demyelinating polyradiculoneuropathy, Morvan syndrome and myasthenia gravis. J Neurol Neurosurg Psychiatry 82(2):230–232. https://doi.org/10.1136/jnnp.2009.174888
80. Lee EK, Maselli RA, Ellis WG, Agius MA (1998) Morvan's fibrillary chorea: a paraneoplastic manifestation of thymoma. J Neurol Neurosurg Psychiatry 65(6):857–862
81. Rubio-Agusti I, Perez-Miralles F, Sevilla T, Muelas N, Chumillas MJ, Mayordomo F, Azorin I, Carmona E, Moscardo F, Palau J, Jacobson L, Vincent A, Vilchez JJ, Bataller L (2011) Peripheral nerve hyperexcitability: a clinical and immunologic study of 38 patients. Neurology 76(2):172–178. https://doi.org/10.1212/WNL.0b013e3182061b1e
82. Laurencin C, Andre-Obadia N, Camdessanche JP, Mauguiere F, Ong E, Vukusic S, Peter-Derex L, Meyronet D, Bouhour F, Vial C, Ducray F, Honnorat J, Petiot P (2015) Peripheral small fiber dysfunction and neuropathic pain in patients with Morvan syndrome. Neurology 85(23):2076–2078. https://doi.org/10.1212/WNL.0000000000002037
83. Nagappa M, Mahadevan A, Sinha S, Bindu PS, Mathuranath PS, Bineesh C, Bharath RD, Taly AB (2017) Fatal Morvan syndrome associated with myasthenia gravis. Neurologist 22(1):29–33. https://doi.org/10.1097/NRL.0000000000000097
84. Torres-Vega E, Mancheno N, Cebrian-Silla A, Herranz-Perez V, Chumillas MJ, Moris G, Joubert B, Honnorat J, Sevilla T, Vilchez JJ, Dalmau J, Graus F, Garcia-Verdugo JM, Bataller L (2017) Netrin-1 receptor antibodies in thymoma-associated neuromyotonia with myasthenia gravis. Neurology 88(13):1235–1242. https://doi.org/10.1212/WNL.0000000000003778