Coexistence of Epilepsy and Myasthenia Gravis: Report of Four Patients and Review of the Literature

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Abstract- Patients with myasthenia gravis (MG) have a higher incidence of epilepsy or seizure disorders than general population. Coexistence of MG and epilepsy seems not simply due to chance association. MG was not infrequently considered as a complication of long-term anticonvulsant therapy. In National Taiwan University Hospital, we found 4 out of 251 MG patients who suffered from epilepsy. MG manifestations of these patients did not differ from those in MG patients without epilepsy. There were increased levels of antibody to acetylcholine receptors and association with thymus hyperplasia or thyroid disease. In the literature, we found 25 reported cases with MG and epilepsy. No specific type of epilepsy was linked to coexistence of MG and epilepsy. Possible causes for MG in association with epilepsy are multiple, including drug-induced depression at the neuromuscular junction, anticonvulsant-related immunological changes, and unknown common mechanism to both diseases.

Key Words: Myasthenia gravis, Epilepsy, Anticonvulsants

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INTRODUCTION

In 1916, Fearnsides described a woman with epilepsy who developed myasthenia gravis (MG) 3 years after the onset of epilepsy[1]. He did not infer any causal relation between these two diseases. In 1953, Pages and Passouant mentioned a male patient who also had both epilepsy and MG, but his MG problems occurred 14 years before the onset of epilepsy[2]. In 1958, Hoefer et al. reported 8 MG patients in association with epilepsy or seizure disorders and noted for the first time a significantly high incidence of epilepsy in MG patients[3]. In 1964, Norris et al. reported 3 epileptic patients with phenytoin overdose who developed disordered neuromuscular transmission[4]. They also demonstrated a toxic effect of phenytoin on the neuromuscular junction in rat experiments. Thereafter, cases with MG and epilepsy were sporadically reported[5-16]. As MG manifestations in these patients usually developed during long-term anticonvulsant therapy and remitted or improved significantly after changing anticonvulsant, MG was thought to be a complication of anticonvulsant therapy[9,15,17,18]. In this report, we described four Taiwanese patients with coexistence of MG and epilepsy, and reviewed literature

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to find the association between these two neurological disorders.

CASE REPORTS

Case 1

SLC, a 46-year-old woman, had several episodes of generalized tonic-clonic convulsions at the age of 4. She received anticonvulsant therapy for 1 year and had had no seizures until the age of 16 when she had recurrence. The seizures were described as sudden head turning and eye deviation to the right side for 15-25 seconds, followed by loss of consciousness and generalized tonic-clonic convulsions for 1-2 minutes. On neurological examination, there were no abnormal findings. An awake EEG revealed focal epileptiform discharges in the left frontal region but isotope brain scans failed to disclose abnormal uptake. She began to receive combined phenobarbital (40~80 mg/day) and phenytoin (100~200 mg/day) therapy. Her compliance was not adequate so that she had occasional attacks, about once or twice a year between the ages of 16 and 33 years. She had complained of mild intermittent weakness of the upper limbs for 2 years since she was 33 years old. The weakness was found most frequently during hair combing and occasionally hand grasping. However, there was neither muscle atrophy nor hyporeflexia. Cranial nerves, coordination, sensations, and sphincter functions were normal, whereas repetitive 3-Hz electric stimulation revealed decremental responses at the right deltoid muscle. The chest computed tomography (CT) showed thymic enlargement. Treatment with pyridostigmine bromide alleviated her weakness. She then received thymectomy, and the pathology revealed lymphoid hyperplasia. After operation, her weakness disappeared gradually and pyridostigmine was discontinued within 3 months. She refused to take anticonvulsants in spite of occasional epileptic attacks. The muscle weakness has since not recurred.

Case 2

SCC, a 57-year-old man, suffered from a severe head injury in a traffic accident when he was 26 years old. At that time, he remained unconscious for 1 week and stayed in a hospital for 3 weeks. Seven months later, the patient developed several episodes of nocturnal tonic-clonic convulsions and was brought to our hospital for further work-up. On examination, there were no abnormal physical or neurological signs. An awake EEG revealed an epileptogenic focus at the right anterior temporal region. Under the diagnosis of post-traumatic epilepsy, anticonvulsant therapy with phenobarbital (80mg/day) and phenytoin (200 mg/day) was started. A follow-up EEG at the age of 34 still disclosed focal spikes in the bilateral temporal regions, although his epilepsy was kept under control. Anticonvulsants were gradually tapered 7 years later and totally discontinued when he was 37 years old.

At the age of 34, the patient suffered from intermittent bilateral ptosis, which could be alleviated by an intramuscular injection of neostigmine methylsulfate. A clinical diagnosis of ocular myasthenia gravis was made. However, his ptosis did not respond to pyridostigmine and double vision occasionally supervened. At his age of 35, the patient received an alternate-day high-dose (100mg) prednisolone. The ptosis and double vision disappeared completely within 1 month but he refused further steroid therapy because of the its side effects. Intermittent ptosis and double vision recurred half a year later. He gradually adapted to the ocular problems and gave up all anti-MG medications at the age of 37.

At the age of 38, about one and a half years after discontinuing anticonvulsant therapy, the generalized tonic-clonic convulsions recurred. The patient was again prescribed phenytoin (300 mg/day) for seizure control. At the same time, his eye problems remained stationary for 2 years. However, ptosis and double vision worsened when he was 41 years of age. Repetitive electric stimulations at the right median and right facial nerves did not show significant decremental responses. Single fiber EMG study at the right extensor digitorum communis muscle showed a mean consecutive difference (MCD) of 97.7 μsec (normal <25 μsec). Pyridostigmine (180mg/day) was restarted and the ocular manifestations partially relieved. The chest CT done at age of 45 was normal. The blood level of anti-acetylcholine receptor (anti-AChR) antibody was 32.13 nmole/L (normal <0.2 nmole/L). Carbamazepine was prescribed to replace

phenytoin, but was abandoned due to leukopenia. Valproates were not considered because of his chronic active hepatitis. Thus, phenytoin was restarted. He kept a stationary condition under phenytoin and pyridostigmine thereafter.

Case 3

SHC, a 33-year-old woman, had an uneventful birth and developmental history. She had her first seizure when she was 10 years old, which was manifested as sudden unawareness to the surroundings, starring for about 30 seconds, followed by automatic behaviors for 1 minute. She also had urine incontinence during the attack. After EEG and neuroimaging studies were performed, a diagnosis of complex partial seizure was made. She was treated with primidone 1250 mg per day. She had no attacks after the age of 19.

At the age of 23, She began to have intermittent general weakness, especially after prolonged working. The weakness was more severe in her proximal limbs and easily relieved by rest. In one month or two, she further developed intermittent ptosis of left eye, dysphagia and masticating difficulty. Myasthenia gravis was diagnosed and treatment with pyridostigmine and high-dose prednisolone was given but in vain. She was hospitalized at the age of 23.

On admission, mild exophthalmos, ptosis and limited upward gaze were found in the left eye. Moderate weakness in the proximal parts and mild weakness in the distal parts of four limbs were detected. There was neither muscle atrophy nor hyporeflexia. Repetitive electric stimulations induced a decremental response at the right deltoid muscle, which disappeared after an intravenous administration of edrophonium. Single fiber EMG study showed an increased MCD (51.4 usec). Chest CT of the mediasternum was normal. The blood level of anti-AChR antibody was 6.24 nmole/L (normal < 0.2 nmole/L). Endocrine study revealed normal thyroid functions but elevated levels of thyroglobulin antibody (1:160, normal < 1:80) and microsomal antibody (1:20480, normal < 1:80). Hashimoto disease was proved via an aspiration cytology study of the thyroid gland. Carbamazepine was prescribed to replace primidone for seizure control and azathioprine to replace prednisolone for MG. Her muscle power then improved after an initial brief worsening.

The patient suffered from recurrence of bilateral exophthalmos and double vision when she was 28 years old. After physical check-up and blood tests, Grave's disease was diagnosed and anti-thyroid drugs were given. She became euthyroid 1 year after the treatment. For relieving her ophthalmopathy, the patient received operations three times between 28 and 30 years of age. Despite the ophthalmological operations, exophthalmos and double vision persisted.

Case 4

DHC, a 43-yea-old woman, began to have recurrent seizures when she was in her junior high school. The seizure manifested as a sudden transient dizzy spell for several seconds with or without subsequent GTC. An EEG revealed interictal regional epileptiform discharges over the right hemisphere with secondary generalization. She was then put under phenytoin therapy (400 mg/day). She had a rather smooth course in the following 30 years and had only one to three seizure attacks per year. However, she began to have intermittent swallowing difficulty and nasal speech at the age of 42. Intermittent double vision, right eyelid drooping and general weakness supervened half a year later. Her weakness could be relieved after rest. On routine physical and neurological examinations, the only abnormal findings were mild right ptosis and mild weakness of neck flexion. The chest CT was normal. The blood level of anti-AChR antibody was 2.91 nmol/L (normal <0.2 nmole/L). MG was diagnosed but pyridostigmine therapy (180 mg/day) failed to alleviate her weakness. Half a year after phenytoin was replaced by sodium valproate, her MG was much improved.

DISCUSSION

Although reported prevalence of epilepsy varied greatly with different methodology and study design, it has been estimated that 0.4%~1.2% of the general population suffer from epilepsy[16]. However, high prevalence rates of epilepsy were found among MG patients[3,11,19,20-23]. In this series, 4 out of 251 MG patients had epilepsy.

Table 1 lists the reported frequencies of epilepsy in various series of MG patients. Cumulative data showed that 2.0% of the MG patients had concomitant epilepsy. Coexistence of MG and epilepsy seems not simply a chance association. EEG abnormality was found in 1.5~5% of the "normal" subjects[24] and epileptiform activity in 2.2~4% of the patients without seizure disorders[25,26]. Whereas EEG abnormality has been reported in around one fourth and paroxysmal EEG changes in one tenth of the MG patients[19,23,27,28](Table 2). The higher frequency of EEG abnormalities in the MG patients than in the normal population implies a subclinical CNS involvement[29]. The fact that MG patients had a higher incidence of paroxysmal EEG changes than the normal control is in good accordance with a higher frequency of epilepsy in MG. In review of the literature, we found 25

Table 1. *Frequency of epilepsy in MG patients in various series*

	Total patients	Epilepsy cases	%
Mortier, et al.[21]	1,969	37	1.9
Nozawa, et al.[19]	41	1	2.4
Snead, et al.[22]	32	4	12.5
Tartara, et al.[23]	118	2	1.7
Rodriguez, et al.[21]	149	4	2.7
Su, et al.	251	4	1.6
Cumulative data	2,560	52	2.0

Table 2. *Frequency of electroencephalographic abnormalities in MG patients in various series*

	Total cases	Abnormal EEG	Paroxysmal changes
Gibbs & Gibbs[27]	14	1	0
Hokkanen & Toivakaka[29]	92	34	19
Nozawa, et al.[19]	22	11	27
Tartara, et al.[23]	118	14	0
Cumulative data	246	60 (24.4%)	25 (10.2%)

Table 3. *Clinical data in patients with myasthenia gravis and epilepsy*

Case no	Sex	Age of onset		Seizure type	AED before MG	MG state after changing AED	Other major medical conditions	Case series
		EPI	MG					
1	M	16	19	GTC	NA	NA		Fearnsides[1]
2	F	48	34	GTC	(MG earlier than EPI)		Thymus hyperplasia at autopsy	Pages, et al.[2]
3	F	35	45	GTC, CPS	PHT	NA	Partial control with PHT &MG -Rx	Hoefer, et al.[3]
4	F	14	24	GTC	PHT, PB	NA	Thymectomy ineffective	Hoefer, et al.[3]
5	F	5	18	GTC, CPS	NA	NA	Various AED drugs with MG-Rx	Hoefer, et al.[3]
6	F	20	23	GTC, CPS	NA	Na	Post-traumatic EP	Hoefer, et al.[3]
7	M	7	17	GTC	MHT, PB	NA	Remission of MG under PHT and MG-Rx	Hoefer, et al.[3]
8	M	4	1 day	GTC	(MG earlier than EPI)		Congenital MG respond to MG-Rx	Hoefer, et al.[3]
9	F	9	30	GTC	PHT	Improved	B12 deficiency; arthritis, PHT overdose	Norris, et al.[4]
10	F	0.3	?	GTC	PHT, PB	Improved	PHT overdose; decremental response (+)	Norris, et al.[4]
11	F	13	24	GTC	PHT	Improved	Measles encephalitis at age 3	Regli, et al.[15]
12	F	0.8	12	PM	PRM	NA	Premature delivery but no anoxia	Sigwald, et al.[36]
13	F	5	8	PM, GTC	PHT, PB	NA		Sigwald, et al.[36]
14	F	9	11	PM	TMD	Improved	Increased Ab to muscle and thymus	Peterson[13]
15	F	10	28	GTC	PHT, PRM	NS	Myasthenic crisis in the puerperium	Peterson[13]
16	F	1.3	7.5	PM, GTC	PB, TMD	Improved	No antimuscular but antinuclear Aby	Booker, et al.[5]
17	F	14	25	PM, GTC	PHT, TMD	Not improved	MG cleared after changing MG-Rx	Gilbert[7]
18	F	6.5	6	PM, GTC	(MG earlier than EPI)		MG much improved with CBZ, PB & MG-Rx	Raynaud, et al.[14]
19	F	2.5	9	PM, GTC	PB, PHT	Not improved	Electrodecremental response (+)	Mortier, et al.[11]
20	F	14	25	GTC	PHT, PB	Improved	Electrodecremental response (+)	Brumlik, et al.[6]
21	F	15	31	GTC	PHT	NA	Thymectomy ineffective	Hansson, et al.[8]
22	M	12	19	PM, GTC	PB, PHT	Not improved	Thymectomy for thymoma	Toivakaka, et al.[18]
23	F	7	35	GTC	PHT	Improved	Neuromuscular block on single fiber EMG	Milonas, et al.[10]
24	F	17	22	CPS	PHT	Improved	Thymus hyperplasia and thymectomy	Lai, et al.[9]
25	M	12	27	CPS	PHT, TMD	Not improved	Psoriasis vulgaris	Kwan, et al.[37]
26	F	16	33	GTC	PHT, PB	Improved	Post-traumatic EPI; increased AChR Ab	Su, et al.
27	M	27	34	GTC, CPS	PHT, PB	NA	Hashimoto disease: increased AChR Ab	Su, et al.
28	F	10	23	CPS	PRM	Improved	Increased AChR Ab	Su, et al.
29	F	13	42	GTC, CPS	PHT	Improved		Su, et al.

EPI: epilepsy; AED: antiepileptic drugs; MG: myasthenia gravis; Rx: treatment; GTC: generalized tonic-clonic convulsions; PM: petit mal; CPS: complex partial seizures; SPS: simple partial seizures; PHT: phenytoin; MHT: mesantoin; PB: phenobarbital; PRM: primidone; TMD: trimethadione; AChR: acetylcholine receptor; Ab: antibody; NA: not available; NS: not significant.

reported cases of MG patients with epilepsy or seizures. Among them, 3 patients had only single epileptic seizure.

Table 3 lists clinical data of the MG patients with epilepsy in the literature including our patients. There were 6 male and 23 female patients, which corresponded well with the sex distribution of MG. Their seizures included generalized tonic-clonic convulsions, petit mal seizures, and complex partial seizures. No specific type of seizure was particularly linked to MG. Most patients listed in Table 3 had an onset of epilepsy earlier than that of MG. Thus, MG conceivably developed during anticonvulsant therapy, though MG was not necessarily a complication of the latter. In most patients, MG did remit after change or cessation of anticonvulsants (Table 3), which implies a causal effect of anticonvulsants on MG.

A variety of anticonvulsants including hydantoins, barbiturates, primidone, and trimethadione have been incriminated in drug-associated MG. Phenytoin has been shown to interfere the neuromuscular transmission in experimental animals[4,30] and in phenyton-treated patients[4,18]. Kaeser recognized that phenytoin was able to aggravate weakness of MG or unmask occult MG[17]. He also noticed that trimethadione could induce a reversible MG in which antithymic, antimuscular and antinuclear antibodies were present[17], which suggests an immunological basis of the anticonvulsant-associated MG[17]. In addition, profiles of the anticonvulsant-associated MG were not clinically or electrophysiologically different from the classical MG. There were increased blood levels of anti-AChR antibody and association with thymoma or thymic hyperplasia which might further suggest the immunological mechanism.

The hypothesis that MG occurs as a result of long-term use of anticonvulsants did not always apply in MG patients with epilepsy (Table 3). As MG might occur earlier than epilepsy and MG did not always remit after change of anticonvulsants, additional mechanisms are necessary to explain the coexistence of these two diseases. Epilepsy is not primarily an immunological disorder, but immunological factors in epilepsy have been suggested[31,32] and immunological concomitants have been well reviewed[33]. Moreover, MG is primarily a disorder at the neuromuscular junction, and anti-AChR antibody has been found in the cerebrospinal fluid in experimental autoimmune MG[34] and in naturally occurring MG[35]. The EEGs of the rabbits with experimental autoimmune MG revealed paroxysmal epileptogenic discharges including spikes, sharp waves, spike- and -wave complex, and polyspike-and-wave complexes[34]. Instead of a causal relation between anticonvulsnats and MG, a common immunological mechanism causing both epilepsy and MG in the same individual could be an alternative explanation for their coexistence.

In conclusion, MG in the epileptics is indistinguishable clinically from the MG not associated with epilepsy. Association of MG with epilepsy may be multi-factorial. Unmasking of an occult MG through anticonvulsant-induced neuromuscular depression, a de novo MG triggered by drug-related immunological disturbances, and an unknown common immune mechanism causing both diseases are all possible factors for the coexistence of MG and epilepsy. However, more immunological studies are necessary to support the hypothesis of immunological bases in epileptogenicity[37].

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