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The Relationship Between GBS and MG: A Systematic Review

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Abstract

Aim: *The aim of our review was to find the association between the two autoimmune conditions Guillain Barre Syndrome and Myasthenia Gravis, whether these have ever coexisted in any patient, possible mechanisms of co-occurrence, the related clinical features, laboratory diagnosis and the treatment modalities for co-occurrence.*

Materials & Methods*: We performed a literature search from PubMed database using the combinations of MeSH terms for Guillain Barre Syndrome and those for Myasthenia Gravis. We included only those papers which were original case reports, published in English language and had the publication dates ranging from 1980-2014. Relevant cross references were also reviewed.*

Results: *A detailed study of 13 case reports (14 cases) was carried out. The age for the concurrence of GBS and MG varied from 17-84 years with most cases in 40-60 year age group. There were 9 male and 5 female patients. Also, among these 14 cases, 6 were Chinese, 3 were Americans, 3 were from Israel, 1 was white and 1 belonged to France. 10 patients had a history of some precipitating factor. All of the 14 patients had areflexia as well as ptosis. Limb weakness, Respiratory failure, opthalmoplegia, dysphagia, dysarthria and facial palsy were other common clinical features.10 out of 14 patients had considerably elevated CSF protein. Nerve conduction and RNS test was abnormal in most cases. 3 patients clearly had evidence of a mediastinal mass. 12 patients were positive for AChR antibody while 4 patients for anti-GQ1b and/or anti-GM. Pyridostigmine, corticosteroids, IVIG, plasmapheresis, immunomodulators were used in various combinations. Although, 2 of them died, prognosis was good in 8 out of 11 recorded patients. Patients, who died, had received treatment either for only GBS or for only MG.*

Conclusions*: All the patients with coexistence syndrome of GBS and MG have areflexia and ptosis. Other clinical and laboratory features may vary in different patients. Treatment modalities used should belong to both the syndromes; otherwise we get a poor prognostic score. We suggest that the concurrence syndrome of GBS and MG occurs due to the antibodies against peripheral nerve (causing GBS) which also attack the neuromuscular junction leading to MG (and/or vice versa) based on enough evidence from literature. We propose that some part of the structure of Ach receptor or postsynaptic membrane at NMJ bears a close relationship to that of myelin sheath of the peripheral nerve and research work at molecular level in this*

context is suggested.

Keywords: *Guillain-Barre Syndrome, Miller Fisher Syndrome, Myasthenia Gravis, Combined, Co-occurrence, Concurrent*

INTRODUCTION

Guilllain Barre Syndrome (GBS) is an immune mediated polyradiculoneuropathy which is acute, severe and fulminant in character [1]. It is believed to result from triggering of immune system by surgery, immunizations, or infections leading to an aberrant immune response that attacks nerve tissue [2].

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder with weakness and fatigability of skeletal muscles as its characteristic features [1].It is caused by the circulating auto-antibodies directed against skeletal muscle receptors and proteins at the neuromuscular junction (NMJ) [3].

Only a few cases have been documented in the medical literature regarding patients having simultaneous occurrence of GBS and MG [4-18]. The estimated annual incidence of GBS in United States is 1.65-1.79/100,000 persons [2] and that of MG is 20/100,000 persons [3]. So, it seems that this concurrence is very rare, however, possible and may be this coexistence remains undiagnosed in many cases due to some clinical features being common in these two syndromes. There have been attempts at explaining the mechanism behind this concurrence but none of them has been proven yet. We reviewed the reports published in English language intensively and also other relevant papers related to the immunopathogenesis of these two syndromes to get a clear look on the mechanism, clinical features, diagnosis and treatment of this concurrence.

METHODS

We performed a systematic review from PubMed database using the combinations of MeSH terms for Guillain Barre Syndrome and those for Myasthenia Gravis. We included only those papers which were original case reports, published in English language and had the publication dates ranging from 1980-2014. After removing the duplicates, a total of only 13 case reports were found which contained details of 14 patients diagnosed with concurrent Guillain Barre Syndrome and Myasthenia Gravis. Relevant cross references were also reviewed.

RESULTS

A total of 15 reports were retrieved in PubMed in which 16 patients were diagnosed as coexistence of GBS and MG [4-18]. 2 case reports were excluded from the study as these were published in languages other than English (French and Spanish) [17,18]. So, a detailed study of 13 case reports (14 cases) was carried out.

The age for the concurrence of GBS and MG varied from 17-84 years with most of the cases falling in the age group of 40-60 years [Figure 1]. Out of all the cases, 9 were male [5-10, 13-15] and 5 female patients [4,11,12, 16], thus, a male preponderance was seen for this concurrence. Also, among these 14 cases, 6 were Chinese [6, 11-

[14], 3 were Americans [9, 10, 15], 3 were from Israel [4,7], 1 was white [8] and 1 belonged to France [5]. While one of the patients had a history of both Upper respiratory tract infection (URI) and Acute gastroenteritis (AGE) [8], 7 of them had URI [5, 6, 9, 11, 12, 14] and 2 had AGE [7, 13], exclusively, as the preceding illness.

The clinical features of these 14 cases are reviewed in Figure 2. All of the patients had areflexia as well as ptosis [4-16]. Limb weakness was observed in 13 cases [4-9, 11-16]. Respiratory failure [5, 7, 8, 11, 12, 14-16] and opthalmoplegia [6, 9-13] was present in 8 cases each. Also cranial nerve palsies were observed as dysphagia [4, 7, 8, 12, 14-16], dysarthria [7, 8, 11, 12, 14, 16] and facial palsy [4, 5, 11, 15] in 7, 6 and 5 patients, respectively.

10 out of 14 patients had considerably elevated CSF protein [5-9, 11-15]. Nerve conduction on examination was found to be abnormal in all patients and RNS test was abnormal in 10 cases [5, 8-16]. No mass in the mediastinum was found on thoracic imaging in 5 patients while 3 patients clearly had evidence of a mass out of which one patient was diagnosed with thymoma [13] and another with thymic hyperplasia [14] and uncertain [5] in the third.

There was positive AChR antibody in 12 cases [4, 5, 7-9, 11-16] including two who were also positive for anti-GQ1b [6, 12] and one who was also positive for anti-GM and anti-GQ1b [8]. One patient was negative for AChR antibody but positive for anti-GQ1b [10]. There was no patient with anti-MuSK antibody.

The treatment modalities used were pyridostigmine, corticosteroids, IVIG, plasmaph-eresis, azathioprine and mycophenolate in various combinations. Although, 2 of them died [5, 7], prognosis was good in 8 out of 11 recorded patients. Patients, who died, had received treatment either for only GBS or for only MG [5, 7].

Figure 1. Age variation in patients having concurrent GBS and MG.

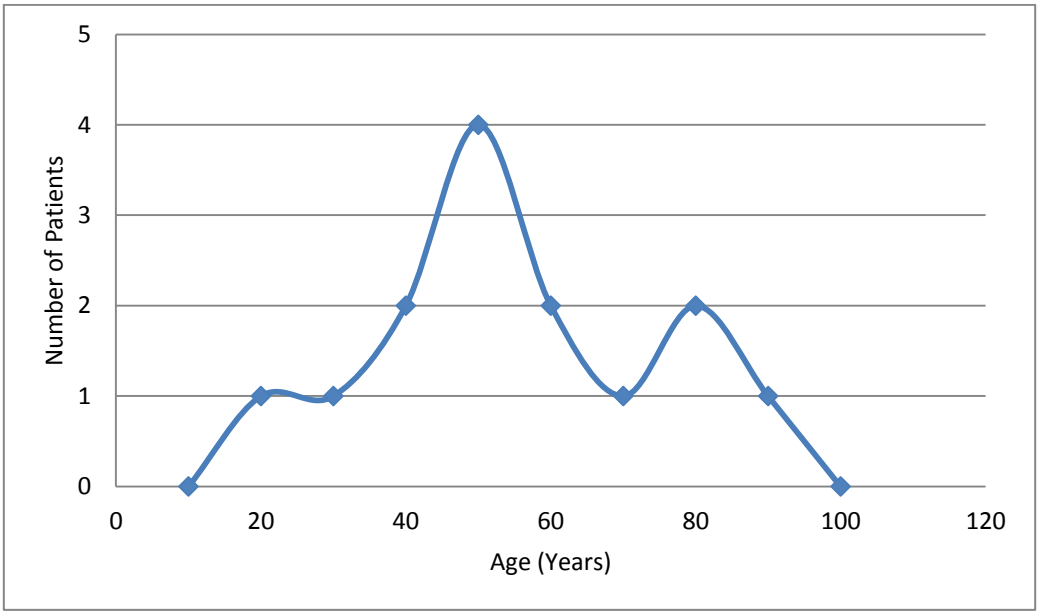

Figure 2. Clinical features of patients with coexisting GBS and MG.

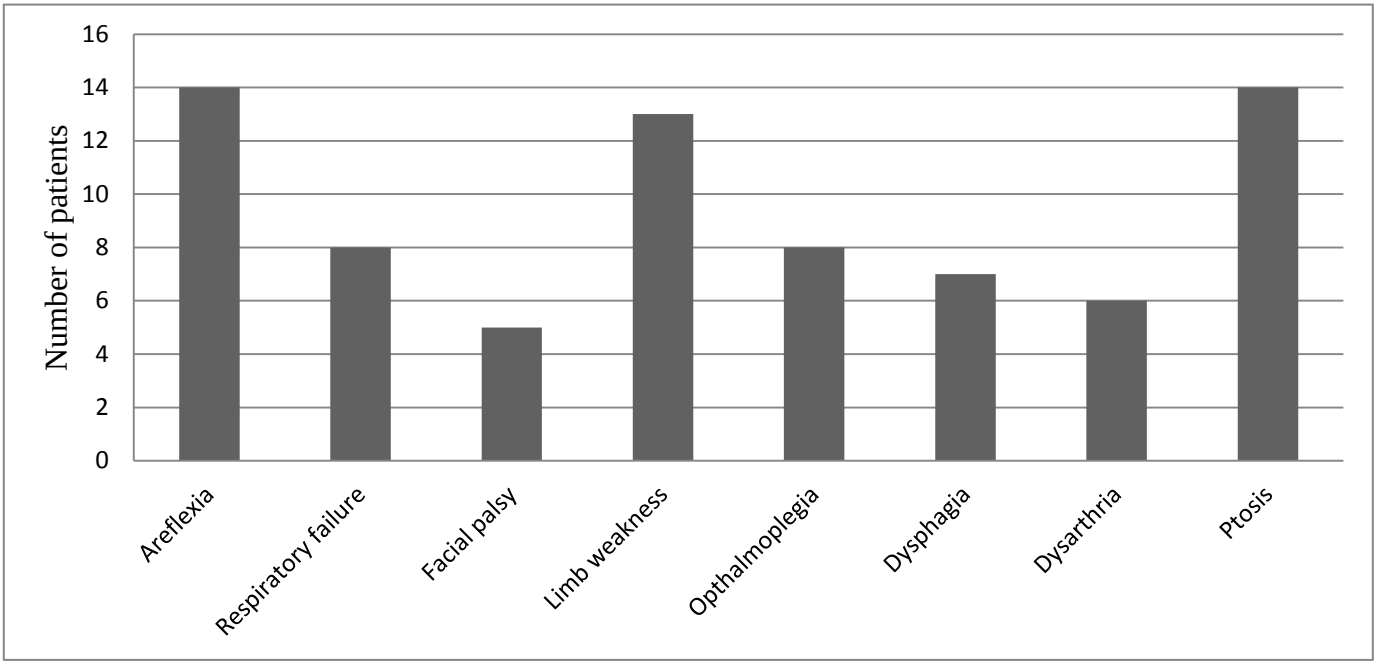

Table 1. Laboratory features of patients with concurrent GBS and MG.

Author (year)	Elevated CSF protein	Abnormal nerve conduction	Abnormal RNS test	Positive ACh-R antibody	Any mediastinal mass
Regev et al. (1982) [4]		+		+	
Regev et al.(1982)[4]		+		+	
Carlander et al. (1991)[5]	+	+	+	+	Yes
Mak et al. (2005)[6]	+	+			-
Farah et al. (2005)[7]	+	+		+	-
Kraus et al.(2007)[8]	+	+	+	+	No
Kizilay et al. (2008)[9]	+	+	+	+	No
Silverstein et al. (2008)[10]		+	+		No
Lau et al.(2009)[11]	+	+	+	+	No
Kung et al.(2009)[12]	+	+	+	+	No
Wang et al.(2011)[13]	+	+	+	+	Thymoma
Hsieh et al.(2012)[14]	+	+	+	+	Thymus Hyperplasia
Isha et al.(2012)[15]	+	+	+	+	-
Zhang et al.(2013)[16]	-	+	+	+	-

Table 2. Treatment plans and related prognostic scores of patients having GBS and MG. [a]Functional outcome was ranked according to the adopted scale by Hughes, characterized as: 0, healthy; 1, minor symptoms or signs, able to run; 2, able to walk >5 m without assistance, butunable to run; 3, able to walk >5 m with assistance; 4, bed- or chair-bound; 5, requiring assisted ventilation for at least part of the day, and 6, dead Abbrevations: IVIG= Intravenous immunoglobulin

Type of therapy	Name of drug/ treatment	Average functional outcome[a]
Mono therapy	Pyridostigmine (alone)[5]	6
	IVIG (alone)[11]	1
Bi therapy	Pyridostigmine + Plasmapheresis[6]	1
	IVIG + Plasmapheresis[7]	6
Tri therapy	Plasmapheresis + Pyridostigmine + Steroids[12]	0
	IVIG + Pyridostigmine + Steroids[9,14,16]	2-3
Quadruple therapy	IVIG + Pyridostigmine + Steroids + Azathioprine[8,13]	1

DISCUSSION

The simultaneous occurrence of GBS and MG on the same patient is really rare with only 16 cases reported in the literature. GBS has been reported to affect adults more frequently than children in Western countries [1]. The peaks of incidence of MG occur in women in their twenties and thirties and in men in their fifties and sixties [1]. In our study, we found that the peak age of occurrence of this concurrent syndrome of GBS and MG was 40-60 years. It has however been reported in a wide range of age groups (17-84 years) with 71.4% of the patients above 40 years of age. [Figure 1]

While males are at slightly higher risk for GBS than females, women are affected with MG more frequently than men, in a ratio of 3:2 [1]. In our study, we found that 64.28% of the cases had male predominance for the coexistence of GBS and MG.

The variants of GBS have different rates of prevalence in different countries, but on the whole, GBS is present worldwide [19]. The prevalence of MG in world shows even wider variation, i.e. ranging from 50/1,000,000 in Hong Kong to 200/1,000,000 in Virginia (USA) as per a study conducted in 2006 [23]. We found that the highest prevalence of this concurrence syndrome was in China with 42.86% of 14 cases.

Although the precipitating factors for Myasthenia gravis are not completely defined [1], GBS is often initiated by infections, vaccines or surgeries [2]. 71.43% of our cases had either URI or AGE or a

combination of the two as the precipitating factors.

The main clinical features of GBS are progressive weakness of more than one limb (also trunk, bulbar, and facial muscles, and/or external ophthalmoplegia) and areflexia. The supportive features include progression of symptoms, relative symmetry of symptoms, cranial nerves and autonomic nervous system involvement, elevated protein with cell counts, afebrile, electromyogram (EMG) and nerve conduction abnormalities consistent with GBS, mild sensory deficits, and finally a halt in the progression of the disease and a clear recovery [15].

On the other hand, the patients who have MG present with a weakness in the ocular, bulbar, limb, and/or respiratory muscles. In some cases, only ocular symptoms (ptosis, diplopia) may be present, while others may have more generalized symptoms. The weakness in MG varies in severity and in location from patient to patient. To begin with, the patient will experience a relapsing- and remitting-type pattern; but as the disease progresses, the symptoms persist, although they still may fluctuate in severity. Also, the limb weakness experienced by MG patients is typically proximal, and the arms often appear to be affected more by the disease than the legs [15].

The symptoms of this concurrent GBS and MG syndrome were typical. All of the 14 patients had areflexia (characteristic of GBS) and ptosis (characteristic of MG). Limb weakness was observed in 92.85% of cases. Other symptoms included Respiratory failure (57.14%), opthalmoplegia (57.14%), dysphagia (50%), dysarthria (42.86%) and facial palsy (35.71%).

Diagnosis of GBS is based on clinical features, cerebrospinal fluid testing, and nerve conduction studies. CSF testing shows increased protein levels but a normal white blood cell count. Nerve conduction studies show a slowing, or possible blockage, of conduction [2] 71.43% of our cases had considerably elevated CSF protein. Nerve conduction on examination was found to be abnormal in 100% cases. Also, three patients were positive for anti-GQ1b and one was positive for both anti-GM and anti-GQ1b.

In addition to the fact that clinical features of the cases of our study resembled to those of MG as well, 85.71% of our cases tested positive for Anti AChR antibody. As MG may be associated with a thymoma/thymus hyperplasia [11], 3 out of 8 patients, who had undergone thoracic imaging, clearly tested positive for a mediastinal mass. There was also a decrement in RNS in 71.43% of the cases.

The treatment modalities used were pyridostigmine, corticosteroids, IVIG, plasmapheresis, azathioprine and mycophenolate. Mostly, treatments for both GBS and MG were used in various combinations and prognosis was good in 8 out of 11 recorded patients. Two patients, who died, had received treatment either for only GBS or for only MG.

There is circumstantial evidence suggesting that GBS results from immune responses to nonself antigens (infectious agents, vaccines) that misdirect to host nerve tissue through a resemblance-of-epitope (molecular mimicry) mechanism [1]. The underlying defect in Myasthenia gravis is a decrease in the number of available acetylcholine receptors (AChRs) at

neuromuscular junctions due to an antibody-mediated autoimmune attack [1]. We suggest that the concurrence syndrome of GBS and MG occurs due to the antibodies against peripheral nerve (causing GBS) which also attack the neuromuscular junction leading to MG and/or vice versa.

According to a study conducted by Burnwald et al, it was clear that IgG antibodies to GQ1b in MFS depress the quantal end plate current release process. They suggested that this most probably occurs by interference of antibodies with presynaptic Ca^{2+} inflow or by interaction with proteins of exocytotic apparatus. Thus, the activation of post synaptic channels is prevented and leads to muscle weakness [20].

Then, in the year 2000, Bullens RW et al performed control experiments in mice proving the binding of anti-GQ1b antibody at the NMJ [21]. As per Krampfl et al (in 2003), the IgG of GBS patients had an, although reversible, but significant blocking action on embryonic and adult type nicotinic AChR channels. This postsynaptic blocking action is similar to that seen in autoimmune myasthenia [22].

In our study, 3 out of 14 patients had clear cut evidence of a mediastinal mass. Thymoma/thymus hyperplasia can be a common cause of MG and other autoimmune disease and may also play a role in initiating the autoimmune process. With thymoma/thymus hyperplasia, there may be low titre of antibodies which are not sufficient to let MG manifest fully clinically. Nevertheless, if an infection occurs, it may not only lead to autoantibodies causing GBS (by molecular mimicry), but it may also enhance the production of AChR antibodies leading to MG [11].

Other important evidence supporting our hypothesis is that of the infection with West Nile Virus (WNV). Ahmed S et al in 2000 reported a case of GBS after infection with West Nile Virus [24]. In 2014, Leis AA et al reported 6 cases that developed MG several months after WNV infection [25]. Thus, it is clear that there is a close link at molecular level in the pathogenesis of GBS and MG. So, it is not shocking to see this concurrence syndrome and in fact, we should look for the features of MG whenever GBS is fully diagnosed and vice versa. The patients who were treated with drug regimen(s) of only one of these syndromes had a very poor prognostic score.

Interferons (IFNs) are substances produced by host cells when a virus infects the host. They have antiviral, antimitogenic, and immunostimulatory effects [27]. There are case reports describing therapeutic pegylated interferon induced GBS [26] and even MG [27], thus, implying that there is a relationship between the antibodies produced in both diseases that may lead to this concurrence syndrome.

Thus, we propose that some part of the structure of Ach receptor or postsynaptic membrane at NMJ bears a close relationship to that of myelin sheath of the peripheral nerve. It is suggested that research work in this regard should be conducted at the molecular level to study in detail these structures and their interaction with the antibodies found in the two syndromes.

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