Case Report

iMedPub Journals
www.imedpub.com

Annals of Clinical Nephrology

2017
Vol.1 No.1:2

DOI: http://www.imedpub.com/annals-of-clinical-nephrology/

# A Case of Generalized Myasthenia Gravis with Membranous Nephropathy

**Elkhatib M[1], Abdalla A[1*] and Mahmoud H[2]**

[1]Department of Internal Medicine and Nephrology, Cairo University, Giza, Egypt

[2]Department of Internal Medicine, Fayoum University, Faiyum, Egypt

[*]**Corresponding author**: Ahmed Abdalla, Department of Internal Medicine and Nephrology, Cairo University, Giza, Egypt, Tel: 20235676105, E-mail: drahmedabdalaa@hotmail.com

**Rec date**: October 27, 2017; **Acc date**: November 09, 2017; **Pub date**: November 13, 2017

**Citation**: Elkhatib M, Abdalla A, Mahmoud H (2017) A Case of Generalized Myasthenia Gravis with Membranous Nephropathy. Ann Clin Nephrol Vol.1: No.1: 2.

## Abstract

We report a 43-year-old woman with bilateral partial ptosis, complete external ophthalmoplegia, and proximal limb weakness. She was found to have generalized myasthenia gravis and membranous nephropathy with normal renal functions. Her myasthenic symptoms and signs improved within 2 months on treatment with pyridostigmine. The occurrence of glomerulonephritis is usually not considered to possibly accompany the course of MG and therefore, myasthenia gravis with membranous nephropathy was considered a rare association. Twenty-four other cases of nephrotic syndrome associated with thymoma and myasthenia gravis have been reported in the literature, many of them were having membranous nephropathy and thus we support the notion that this form of glomerulonephritis is among the most frequently associated with MG. Most reported cases were related to thymic abnormality or thymectomy. However, our patient was neither thymectomized nor having thymoma. It is postulated that either thymic hyperplasia- with normal sized thymus- or subclinical stage of a thymoma may be the underlying aetiological factor in this patient.

**Keywords:** Nephropathy; Myasthenia gravis; Pyridostigmine; Glomerulonephritis; Thymic hyperplasia

## Introduction

Myasthenia gravis is an autoimmune syndrome that is rarely associated with glomerulonephritis [1]. The types of glomerulonephritis with described in association myasthenia gravis include minimal change disease, focal segmental glomerulosclerosis and membranous nephropathy [2]. We report here a patient with generalized myasthenia gravis and membranous nephropathy.

## Case Report

A 43-year-old Egyptian woman with free medical history, presented with a 4 weeks' history of involuntary closure of both eyes and diplopia. The condition was also associated with dysphagia and fatigable chewing.

Examination revealed bilateral partial ptosis and bilateral complete external ophthalmoplegia. Muscle power was reduced to grade IV in abductors and extensors of both arms. All tendon reflexes were normal.

The diagnosis of myasthenia gravis was confirmed by a positive acetylcholine receptor antibody assay. EMG however showed no decremental response in facial muscles by repetitive nerve stimulation and single fibre electromyogram was not available locally.

Ptosis and external ophthalmoplegia showed complete improvement after about 2 months of pyridostigmine. The patient became completely free of myasthenia gravis symptoms on a pyridostigmine dose of 60 mg four times daily.

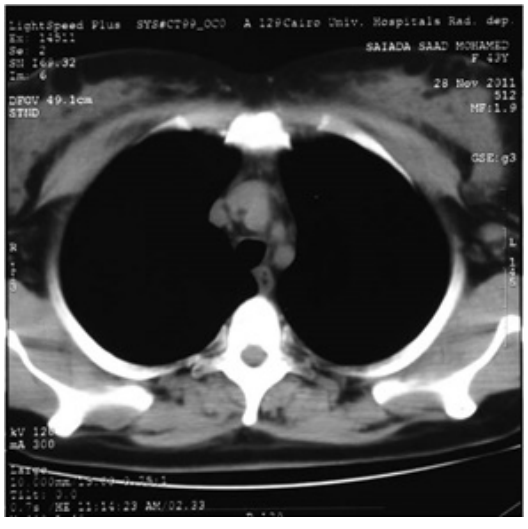

**Figure 1** CT scan of the thorax showing normal thymus tissue.

One year later, the patient started to develop puffiness of eyelids together with bilateral lower limb oedema. In addition, myasthenic symptoms relapsed again and that is why she started oral prednisolone therapy at a dose of 30 mg daily. Urine analysis revealed a urinary protein excretion of 3.6 g/

day. Creatinine clearance was normal (110 ml/min). There was hypoalbuminaemia (serum albumin was 2.1 gm%), hypercholesterolaemia (serum cholesterol was 707 mg%) and hypertriglyceridemia (seum TG level was 463 mg%). Renal ultrasound scan revealed normal sized kidneys with increased cortical echogenicity. Renal biopsy established early membranous nephropathy by light microscopy. Electron microscopy confirmed the light microscopic findings and revealed also thickening of GBM by subepithelial electron-dense deposits separated by spikes of GBM material and diffuse fusion of epithelial cell foot processes was also noted. CT scan of the thorax showed normal thymus tissue **(Figure 1)**. The ESR was 110 mm/hour. Antinuclear antibodies, rheumatoid factor, and hepatitis B, hepatitis C, and HIV antibodies were negative. C3 and C4 serum levels were normal. Screening for malignancy with stools for occult blood, CT abdomen, CEA and CA 125 were negative.

## Discussion

Myasthenia gravis is the most common disorder of neuromuscular transmission. It is now one of the best characterized and understood autoimmune disorders. The hallmark of the disorder is a fluctuating degree and variable combination of weakness in ocular, bulbar, limb, and respiratory muscles [3].

Weakness is the result of an antibody-mediated, T-cell dependent immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors or receptor-associated proteins) [4].

The diagnosis of myasthenia gravis can be established by clinical (e.g. edrophonium {Tensilon} test) and serologic testing (e.g. Acetylcholine receptor antibodies) [4].

Electrodiagnostic studies are also an important supplement to the immunologic studies and may also provide confirmation of the diagnosis of myasthenia. Repetitive nerve stimulation (RNS) studies and Single-Fiber Electromyography (SFEMG) have a diagnostic sensitivity in generalized myasthenia of about 75% and 95%, respectively [5].

RNS studies are positive in about 75% of patients with generalized myasthenia if recordings are made from proximal (usually trapezius and orbicularis oculi), as well as distal muscles and this may explain the absence of decremental response in our patient. RNS studies are positive in approximately 50% of patients with ocular myasthenia [5].

It is postulated that all patients with myasthenia have B cells that produce AChR-Ab in the thymus. In addition, 75% of patients with myasthenia have thymic abnormalities. Thymic hyperplasia is most common (85%), but various tumors (primarily thymoma) are present in up to 15%. The thymic tumors are usually noninvasive cortical thymomas, but invasive thymic carcinoma can occur [6].

Myasthenia gravis can be considered a paraneoplastic effect of thymoma, but not of extrathymic tumors. Nonetheless, myasthenia has been associated with extrathymic tumors, such as small cell lung cancer and Hodgkin lymphoma [7].

The occurrence of glomerulonephritis is usually not considered to possibly accompany the course of MG and therefore, myasthenia gravis with membranous nephropathy is considered a rare association [8].

Supporting this view may be the finding that among 12 large series reviewed by Oosterhuis, including almost 4,090 patients, only five cases associated with glomerulonephritis were found (0.12%) [9]. Of these, three were mentioned without details about the type of the glomerular disease [10] and two as just ‘‘acute nephritis’’ [11] and ‘‘membranous nephropathy.’’ [12].

Conversely, a case of ‘‘acute glomerulonephritis’’ was found in 1 of 32 myasthenic children by Snead et al, [13] and 10 adult cases of glomerulonephritis associated with MG have been described in recent years by different authors [14] **(Table 1)**.

Zbiti and colleagues mentioned that Twenty-four cases of nephrotic syndrome associated with thymoma and myasthenia gravis have been reported in the literature.

**Table 1** Main clinical findings of patients with glomerulonephritis and myasthenia gravis.

| Author | Scadding et al. [15] | | | Miyazaki et al. [16] | | | Chan et al. [17] | | Innes et al. [18] | Haslam et al. [14] | Valli et al. [1] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients (sex, age) | 1 (M, 48) | 2 (F, 64) | 3 (F, 61) | 1 (M, 58) | 2 (F, 32) | 3 (M, 30) | 1 (F, 57) | 2 (F, 37) | 1 (M, 25) | 1 (M, 36) | 1 (M, 50) | 2 (M, 80) | 3 (F, 30) |
| Duration of MG (yrs.) | 14 | 8 | 4 | 1‡ | 1‡ | 1‡ | 3 | 3 | 5 | 0§ | 15 | 9 | 2 |
| Thymoma/ Thymectomy* | yes/ no (12) | yes/yes (3) † | yes/yes (,1) | no/ no | yes/ yes | no/ yes | yes/ yes (14) | yes/ yes (3) | no/yes (,4) | no/no | yes/yes (14) | yes/yes (9) | no/yes (same time) |
| Autoantibodies | AchR, SM | AchR, SM/ MicroS | AchR, SM | NE | AchR, ANF | Absent | ANF | Absent | Absent | AchR, Thyroid | NE | AchR, ANF, SM | AchR, ANF |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Immunosuppressants at the discovery of GN | yes | yes | yes | no | no | no | no | no | yes | No | yes | yes | no |
| GN | FSGS | MCD | Focal proliferative | IgAN | IgAN | IgAN | MCD | MCD | SHP nephritis | Membranoproliferative | Membranous | Extracapillary | Membranous |
| Plasma Creatinine (mg/dL) | 37 (urea, mg%) | 63 (urea, mg%) | 29 (urea, mg%) | 1.7 | 1.7 | 2.4 | 1.5 | 0.8 | 0.9 | 55 ml/min (Creatinine clearance) | 1.3 | 11.5 | 0.8 |
| Proteinuria (g/24 hrs) | 23.7 | 10.5 | 17.8 | 0.5 | 0.5 | 1.5 | 27 | 7 | 0.2 | 13 | 3.4 | 1.5 | 3.8 |

*Numbers in parentheses indicate the interval in years from thymectomy to the discovery of the renal disease.

†: At the time of the discovery of glomerulonephritis, pleural deposits with the same histology as the thymoma.

‡: Glomerulonephritis preceded MG.

§: MG and glomerulonephritis at the same time.

Abbreviations: FSGS: Focal Segmental Glomerulosclerosis; SHP: Scho¨Nlein-Henoch Purpura; Achr: Acethylcoline Receptors; SM: Striated Muscle; Micros: Microsomal; ANF: Antinuclear Factors; NE: Not Evaluated

In most of the patients, MG usually preceded glomerulonephritis by a number of years, although in three cases glomerulonephritis developed first, [17] and in another patient the renal disease and MG were diagnosed at the same time [14]. Eight patients had undergone thymectomy, six of whom for a thymoma, 1 to 14 years before glomerulonephritis.

Autoantibodies, mainly against AchR, striated muscle, and nuclear factors, were a frequent finding. Of note, four patients were receiving corticosteroids or cytotoxic agents for their MG when glomerulonephritis developed. Renal biopsy showed several types of glomerulonephritis, which were associated with various clinical presentations, including nephrotic syndrome and renal failure. After renal biopsy, six patients were treated for their renal disease and four were not **(Table 2)**. Two treated patients did not respond to corticosteroids alone [17] or in association with cytotoxic agents [15].

**Table 2** Treatment and outcome of renal disease.

| Author | Patients | Therapy for the Glomerulonephritis | Outcome |
|---|---|---|---|
| Scadding et al. [15] | 1 | Prednisolone, aza, cyclophosph | Persistent nephrotic syndrome |
| | 2 | Prednisolone (IV and oral) | Complete remission |
| | 3 | Prednisolone, aza, cyclophosph | Proteinuria (1 g/24 hrs) |
| Miyazaki et al. [16] | 1 | nil | Progressive renal failure |
| | 2 | nil | Progressive renal failure |
| | 3 | nil | Progressive renal failure |
| Chan et al. [17] | 1 | Prednisolone | Progressive renal failure and death |
| | 2 | Prednisolone | Complete remission |
| Innes et al. [18] | 1 | nil | Microscopic hematuria and HBP |
| Haslam et al. [14] | 1 | IV methylpred, prednisolone | Proteinuria (2.2 g/24 hrs) |
| Valli et al. [1] | 1 | IV methylpred, pred, cyclophosph, cyA | Renal failure + nephrotic synd. |
| | 2 | IV methylpred, IV cyclophosph | End-stage renal failure |
| | 3 | nil | Proteinuria (1.3 g/24 hrs) |

Aza: Azathioprine; Cyclophosph: Cyclophosphamide; Methylpred, Ethylprednisolone; Pred: Prednisone; Cya: Cyclosporin A; HBP: High Blood Pressure; IV: Intravenous

One other patient had a relapsing course but only mild proteinuria at the last check [15] and three other patients responded to corticosteroids with either partial or complete remission of proteinuria [17].

Of the four untreated patients, three had a progressive renal failure, [16] and one microscopic hematuria and high blood pressure [18].

The three patients described by Valli et al. deserve some comments. Patients 1 and 3 had membranous nephropathy, which was found in another patient before [12].

Thus, this form of glomerulonephritis is among the most frequently associated with MG. Patient 2 had pauciimmune extracapillary glomerulonephritis and a very poor renal outcome, which had not been reported before in patients with MG. Because patient 1 also is at risk of progressive renal disease for persisting nephrotic syndrome and renal failure, the appearance of glomerulonephritis in a patient with MG should be regarded as a potentially ominous event.

Thus, it is possible to suggest a pathogenetic association between the two disorders. Circulating AchR antibodies, which are found in most myasthenic patients, may also react against glomerular antigens, thus causing complement fixation, activation of lytic phase of complement reaction, and membrane attack deposition as they do in the neuromuscular junction [19].

Alternatively, the same events might be caused by immune complexes, containing AchR antibodies or other autoantibodies, penetrating the glomeruli from the circulation. These mechanisms might especially explain the association with membranous, IgA, or membranoproliferative glomerulonephritis, which are considered diseases attributable to immune deposits [20].

Another possible factor may be the thymus gland. Thymoma, which was present in two of our patients and in most of those described by others, [17] can be associated with autoimmune disorders per se [21].

To this purpose, it is of importance that several cases of glomerulonephritis-minimal change disease [22] or membranous nephropathy [23] have been described in patients with thymoma without MG. In these patients, minimal change disease is thought to be due to an impairment of the cellular immunity [24].

Also, thymectomy could have been a factor favoring glomerulonephritis. Thymectomy, which is done in most myasthenic patients with improvement of symptoms, [25] is followed by a number of changes in lymphocyte functions, which may require several years to become evident [26].

This might explain the late occurrence of glomerulonephritis in thymectomized patients. Moreover, thymectomy is regarded as a condition resulting in autoimmune disease, [27] as exemplified best by patients who develop systemic lupus erythematosus [28] or antiphospholipid syndrome after this procedure [29].

It is even possible that the low prevalence of glomerulonephritis in MG found by Oosterhuis in his review reflected the fact that thymectomy was much less frequently performed before the 1980s than it is today [9].

Both myasthenia gravis and membranous nephropathy are mediated via immunoglobulin G and the membrane attack complex of the complement system. The most likely common link that triggers the autoimmune response is the abnormal thymus gland. Autoimmune diseases result from an imbalance between autoreactive lymphocytes and immunoregulatory mechanisms [2].

As the thymus gland suppresses the immune response against autoantigens, when its function is compromised, autoimmune syndromes may result. Two patients with the combination of myasthenia gravis and membranous nephropathy had thymomas [30]. Two others had thymic hyperplasia [8].

In one patient both disorders showed improvement after thymectomy favoring the possible aetiological role of the deranged thymus [8].

When associated with nephropathy, thymoma is known to be discovered several years after the diagnosis of glomerulonephritis, but thymic hyperplasia can occur with a normal sized thymus gland. It is likely that our patient with myasthenia gravis and membranous nephropathy has either thymic hyperplasia or a subclinical stage of thymoma.

## Conclusion

We conclude that glomerulonephritis can be listed among the immunologic disorders associated with MG. Clinically, glomerulonephritis can be mild or severe, requiring or not a specific treatment, to which some patients may respond with a complete recovery. Further studies are necessary to better elucidate the pathogenetic mechanisms linking glomerulonephritis and MG, especially the role of thymectomy in view of its possible effects in favoring autoimmunity.

## Acknowledgements

We thank Prof. Dr. Sawsan Fadda for providing the renal biopsy images.

## References

1. Valli G, Rogazzi GB, Cappellari A, Rivolta E (1998) Glomerulonephritis associated with myasthenia gravis. Am J Kidney Dis 31: 350-355.
2. Karras A, Montpreville V, Fakhouri F, Griinfeld J, Leasavre P (2005) Renal and thymic pathology in thymomaassociated nephropathy: Report of 21 cases and review of the literature. Neph Dial Transplant 20: 1075-1082.
3. Drachman DB (1994) Myasthenia gravis. N Engl J Med 330:1797.
4. Keesey JC (2004) Clinical evaluation and management of myasthenia gravis. Muscle Nerve 29: 484.

5. Meriggioli MN, Sanders DB (2004) Myasthenia gravis: diagnosis. Semin Neurol 24: 31.
6. Castleman B (1966) The pathology of the thymus gland in myasthenia gravis. Ann NY Acad Sci 135: 496.
7. Levin N, Abramsky O, Lossos A (2005) Extrathymic malignancies in patients with myasthenia gravis. J Neurol Sci 237:39.
8. Matsluda M, Miki J, Tabata K, Ikezoe M, Nishizawa N, et al. (2000) Myasthenia gravis with membranous nephropathy, successfully treated with extended total thymectomy. Internal Medicine 39: 490-494.
9. Oosterhuis HJGH (1984) Myasthenia gravis. New York, NY, Churchill Livingstone, USA. pp. 115-122.
10. Osserman KE (1958) Myasthenia gravis. New York, NY, Grune & Stratton, USA. p. 248.
11. Turner JWA (1974) Myasthenia gravis. Proc R Soc Med 67: 763-769.
12. Pirskanen R (1977) Genetic aspects in myasthenia gravis: A family study of 264 Finnish patients. Acta Neurol Scand 56: 365-388.
13. Snead OC, Benton JW, Dwyer D, Morley BJ, Kemp GE, et al. (1980) Juvenile myasthenia gravis. Neurology 30: 732-739.
14. Haslam PJ, Proctor SJ, Goodship THJ, Zouvani J (1993) Immunecomplex glomerulonephritis, myasthenia gravis and compensated hypothyroidism in a patient following allogenic bone marrow transplantation. Nephrol Dial Transplant 8: 1390-1392.
15. Scadding GK, Sweny P, Wilson SG, Havard CVK, Newson-Davis J (1983) Glomerulonephritis, thymoma and myasthenia gravis. Q J Med 52: 187-193.
16. Miyazaki M, Kimura N, Imai K, Eguchi K, Yagame M, et al. (1989) Association of IgA nephropathy and myasthenia gravis. Nephron 52: 402-404.
17. Chan PC, Lau CC, Cheng IK, Chan KW, Jones BM, et al. (1990) Minimal change glomerulopathy in two patients after thymectomy. Singapore Med J 31: 46-47.
18. Innes A, Coton RE, Burden RP (1990) Association of IgA nephropathy and myasthenia gravis. Nephron 54: 354.
19. Sahashi K, Engel AG, Lambert EH, Howard FM (1980) Ultrastructural localization of the terminal and lytic complement component (C9) at the motor end-plate in myasthenia gravis. J Neuropathol Exp Neurol 39: 160-172.
20. Fazekas A, Komoly S, Bozsik B, Szobor A (1986) Myasthenia gravis: Demonstration of membrane attack complex in muscle end-plate. Clin Neuropathol 5: 78-80.
21. Souadjian JV, Enriquez P, Silverstein MN, Pe´pin JM (1974) The spectrum of diseases associated with thymoma: Coincidence or syndrome? Arch Intern Med 134: 374-379.
22. Ogawa M, Ueda S, Ohto M, Kono N, Itami J, et al. (1992) Minimal-change nephrotic syndrome developed after non-surgical treatment of a thymoma. Clin Nephrol 38: 171-172.
23. Posner MR, Prout MN, Berk S (1980) Thymoma and the nephrotic syndrome: A report of a case. Cancer 45: 387-391.
24. McDonald P, Kalra PA, Coward RA (1992) Thymoma and minimal change glomerulonephritis. Nephrol Dial Transplant 7: 357-359.
25. Valli G, Jann S, Premoselli S, Scarlato G (1987) Myasthenia gravis treatment: Twelve years' experience on 110 patients. Ital J Neurol Sci 8: 93-101.
26. Wijermans P, Oosterhuis HJGH, Astaldi GCB, Schellekens PTHA, Astaldi A (1980) Influence of adult thymectomy on immunocompetence in patients with myasthenia gravis. J Immunol 124: 1977-1982.
27. Weinberg K, Parkman R (1995) Age, thymus, and T lymphocytes. N Engl J Med 332: 182-183.
28. Mevorach D, Perrot S, Buchanan NMM, Khamashta M, Laoussadi S, et al. (1995) Appearance of systemic lupus erythematosus after thymectomy: Four case reports and review of the literature. Lupus 4: 33-37.
29. Shoenfeld Y, Lorber M, Yucel T, Yazici H (1997) Primary antiphospholipid syndrome emerging following thymectomy for myasthenia gravis: Additional evidence for the kaleidoscope of autoimmunity. Lupus 6:474-476.
30. Tomida C, Yamagata K, Ishizu T, Nakajima M, Doi M, et al. (1999) A case of nephritic syndrome associated with myasthenia gravis and malignant thymoma. Nippon Jinso Gakkai Shi 41: 77-82.