A Case of Generalized Myasthenia Gravis with Membranous Nephropathy

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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 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.
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 (serum 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.

The occurrence of glomerulonephritis is usually not considered to possibly accompany the course of MG and therefore, myasthenia gravis with membranous nephropathy is 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.

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].

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

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</thead>
<tbody>
<tr>
<td>Patients (sex, age)</td>
<td>(M, 48)</td>
<td>(F, 64)</td>
<td>(F, 61)</td>
<td>(M, 58)</td>
<td>(F, 32)</td>
<td>(M, 30)</td>
</tr>
<tr>
<td>Duration of MG (yrs.)</td>
<td>14</td>
<td>8</td>
<td>4</td>
<td>1†</td>
<td>1†</td>
<td>1†</td>
</tr>
<tr>
<td>Thymoma/Thymectomy*</td>
<td>yes/no (12)</td>
<td>yes/yes (3)</td>
<td>yes/yes (1)</td>
<td>no/yes</td>
<td>yes/yes (14)</td>
<td>yes/yes (3)</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>AChR, SM</td>
<td>AChR, SM/ MicroS</td>
<td>AChR, SM</td>
<td>NE</td>
<td>AChR, ANF</td>
<td>Absent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chan et al. [17]</th>
<th>Innes et al. [18]</th>
<th>Haslam et al. [14]</th>
<th>Valli et al. [1]</th>
</tr>
</thead>
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</tr>
</tbody>
</table>
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.

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

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

*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: Schönlein-Henoch Purpura; Achr: Acetylcoline Receptors; SM: Striated Muscle; Micros: Microsomal; ANF: Antinuclear Factors; NE: Not Evaluated
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 glomerulonephritides 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 aetiologic 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

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References