Late-Onset Myasthenia Gravis

A Changing Scene

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The prevalence of myasthenia gravis (MG) among middle-aged and older patients has increased. Patients with early-onset MG live longer than before, but there is also an increase in late-onset MG (onset of the disease after the age of 50 years in patients with no clinical or paraclinical evidence of a thymoma). Epidemiological data support using the age of 50 years to separate early- and late-onset MG. The main immunological difference between early- and late-onset MG is the presence of antibodies to muscle titin, which are detected in approximately 50% of patients with late-onset MG. Treatment of late-onset MG has to be tailored both to the age of the patient and to the immunological findings of that particular form of MG.

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The disease occurs, for the most part, in the third decade, and is rare before the age of 15, or after 70. In approximately 60 per cent of the patients the disease develops between the ages of 20 and 40.

The concept that myasthenia gravis (MG) mainly affects young adults and is uncommon after the age of 50 years was based on clinical experience and supported by epidemiological data. In 1900, when Campbell and Bramwell surveyed the literature and added 1 case of their own, they identified 60 cases, 3 of which involved patients who were older than 50 years at the onset of their disease. By 1953, Schwab and Leland reported that 62% of women and 27% of men with MG were younger than 30 years at the onset of the disease. The corresponding figures reported by Simpson et al in 1960 were 49% women and 23% men. In both studies, the disease was uncommon among younger men, with the majority of male patients being older than 60 years. Men with MG formed 2 groups: one with the peak age at onset between 25 and 35 years and the other between 60 and 70 years. These observations were reflected in standard textbooks of neurology.

Today, some 40 years later, the onset of MG occurring after the age of 50 years is not uncommon. Recent studies have shown an increased prevalence of the disease among middle-aged and older patients. This may be the result of both an improved prognosis and a more advanced medical diagnosis among elderly patients. Certainly, most patients with MG receive better treatment today and have a longer life span than ever before. However, the data suggesting a higher prevalence of MG cannot be explained by an accumulation of patients with early onset of the disease who live longer, although in the 1990s the life expectancy of patients with early-onset MG who have undergone a thymectomy does not differ from that of the normal population.

There are also a substantial number of patients who develop the disease much later in life. Three recent studies, from western Denmark, central and western Virginia in the United States, and Croydon, Great Britain, have demonstrated an increased incidence of MG in the elderly population. In a Dutch study of 100 consecutive patients with MG who were referred between 1985 and 1989, 33% were older than 50 years at the onset of the disease. In an epidemiological study from central and western Virginia, the prevalence was significantly higher in individuals older than 50 years. Moreover, when prevalence rates were analyzed, the figures for MG showed an increase over time, compared with rheumatoid arthritis and systemic lupus erythematosus, for which trends were static.

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Myasthenia gravis has traditionally been regarded as a disorder of young women and older men. The incidence of MG is still higher among younger women than it is among young men, but recent studies have demonstrated that both sexes now show a bimodal curve for age at onset of MG.\(^5,12,13\) The age peak for late-onset MG (onset after the age of 50 years) is now the same for both sexes, between 70 and 80 years, mainly because of a relative increase in the disease among older women.\(^14\) Using linear regression techniques, Phillips\(^15\) has calculated that 61.3% of all patients with MG in the United States are now older than 50 years.

The age structure of the population of western societies is changing. Thirty-two percent of the population in the countries of the European Union are older than 50 years.\(^16\) A similar aging process is taking place in the population of the United States.\(^17\) An expansion of the age group from which late-onset MG is recruited will in itself lead to an increase in the number of patients. Neurologists will therefore see more patients with late-onset MG than ever before.

When does late-onset MG start? Compston et al.\(^18\) in their 1980 study, suggested 40 years of age as an arbitrary division.Somnier et al.\(^19\) have pointed out that incidence data are more in favor of separating early- and late-onset MG at the age of 50 years. Late-onset MG is defined herein as the onset of the disease after the age of 50 years in a patient with no clinical or paraclinical evidence of a thymoma but, quite often, with immunological findings similar to those found in patients with thymoma.\(^19\)

Is late-onset MG different from early-onset MG? Yes, in many respects. Thymoma is much more common among middle-aged and older patients. But, even late-onset, nonthymoma MG has characteristics that differentiate it from early-onset disease. Patients with early-onset MG are often DR3 positive and show a high frequency of clinical and serological autoimmune overlap. Patients with thymoma-associated MG are never, or almost never, DR3 positive, and this haplotype is also uncommon in late-onset MG.\(^19\) It has therefore been postulated that late-onset MG is a disease that is different from early-onset MG.\(^14,18\)

The neuromuscular symptoms seen in patients with late-onset MG do not differ from those observed in patients with early-onset MG, although the disease is more likely to be more severe in patients in whom MG develops after the age of 50 years.\(^20\) It has been known for a long time that MG with thymoma has a poorer prognosis than MG without thymoma. The difference in prognosis is probably not related to the size of the tumor, since patients with small thymomas may also have a more serious prognosis. Somnier\(^19\) therefore postulated that the severity of the disease is related to immunological factors associated with the thymoma. In his study, removal of a thymoma in MG resulted in an exacerbation of the clinical severity of the disease and an increase in acetylcholine receptor antibody titers.

The majority of patients with MG, whether it be of early or late onset, have circulating antibodies to the acetylcholine receptor, but the concentration is often lower in those with late-onset disease.\(^22,23\) The main immunological difference between early- and late-onset MG is the presence of antibodies to striated muscle antigens, particularly antibodies to titin. These antibodies are found in serum samples from 85% of patients with MG with thymoma and from approximately 50% of those with late-onset MG, but are extremely rare in samples from those with early-onset MG (MG with thymus hyperplasia).\(^20\) The presence of these antibodies is not attributable to disease duration, since there is no relationship between titer and duration of the disease.\(^24\)

Are they simply a phenomenon of aging, since they are not detected among healthy older individuals. Patients with late-onset MG with thymus involution who have striated muscle antibodies are immunologically identical to patients with MG with thymoma.\(^19\) These antibodies are mainly antibodies to titin.\(^25,26\) Disease severity in late-onset nonthymoma MG relates to the presence or absence of antibodies to the titin epitope MGT30. While not related to titer, there is a qualitative association of severity to titin antibodies.\(^27\) Some patients in whom the disease has developed late in life and who do not have titin antibodies may therefore represent a delayed early onset.

Somnier and Trojaborg\(^28\) reported that myopathy is more common in patients with late-onset MG than in those with early-onset MG. They also found that the occurrence of myopathy was associated with the presence of anti-striated muscle (titin) antibodies. Based on their observations, they suggested that the increased weakness seen in some older patients is caused by an immunologically mediated myopathy and that this could to some extent account for the poorer prognosis in patients with late-onset MG.

Treatment of late-onset MG can be difficult. The effect of acetylcholinesterase inhibitors is often temporary. Plasma exchange has more complications in the elderly. Keynes,\(^29\) one of the pioneers of surgical treatment of MG, observed that the results of thymectomy were much poorer in the older age group. He also pointed out, and others have confirmed, that patients with thymoma have a worse prognosis.\(^21,29\) When thymoma cases are excluded, however, the age at onset may not significantly affect the response to thymectomy.\(^30,31\) It is known that some patients with late-onset MG do not improve after thymectomy and that a poorer outcome can be expected if myopathic deterioration already exists. Older patients are especially vulnerable to the many complications of long-term steroid therapy. The choice of immunosuppressive drugs may not be the same as in younger patients. The therapeutic situation in a case of late-onset MG is therefore different from that in a case of early-onset MG, and the treatment offered will have to be tailored both to the age of the patient and to the immunological findings of that particular form of MG.

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