Association between myasthenia gravis and Alzheimer's disease

M. Isabel Morales-Casado, Alba M. Diezma-Martín, Francisco Muñoz-Escudero, Sara Rosenstone-Calvo, Beatriz Mondéjar-Marín, Alfonso Vadillo-Bermejo, Carlos Marsal-Alonso, Pedro Beneyto-Martín

Introduction. Myasthenia gravis (MG) and Alzheimer's disease (AD) are two of the most important diseases where the dysregulation of acetylcholine activity plays a crucial role. In the first, this dysregulation happens at the level of the neuromuscular junction and in the second, in the central nervous system (CNS).

Aim. To analyze the possible relationship between these two pathologies, analyzing the prevalence and the *odds ratio* of AD within patients previously diagnosed with MG. We will compare these data with respect to the prevalence of AD in the general population.

Patients and methods. We examined the data obtained by the electronic medical records of patients in the health care system of Castilla La Mancha using the Natural Language Process provided by a clinical platform of artificial intelligence known as the Savana Manager®.

Results. We identified 970,503 patients over the age of 60 years, of which 1,028 were diagnosed with MG. The proportion of the patients diagnosed with AD within this group (4.28%) was greater than the rest of the population (2.82%) (p = 0,0047) with an *odds ratio* of 1.54 (confidence interval at 95% 1.13-2.08; p = 0.0051) without finding significant differences in the bivariate analysis for the rest of the most important actual known risk factors for AD.

Conclusion. Our results suggest that there might be an increase in the prevalence of AD in patients previously diagnosed with MG.

Key words. Acetylcholine. Alzheimer's disease. Alzheimer's type dementia. Cognitive impairment. Memory. Myasthenia gravis.

Neurology Department (M.I. Morales-Casado, A.M. Diezma-Martín, F. Muñoz-Escudero, S. Rosenstone-Calvo, B. Mondéjar-Marín, A. Vadillo-Bermejo, C. Marsal-Alonso). Research Unit. Hospital Universitario de Toledo, Toledo, Spain (P. Beneyto-Martín).

Correspondence:
Dra. M. Isabel Morales Casado. Servicio de Neurología. Hospital Universitario de Toledo. Avenida del Río Guadiana. E-45007, Toledo, Spain.

E-mail:
mimorales@sescam.jccm.es

ORCID:
0000-0002-7398-0092 (M.I.M.C).

Accepted:
04.12.23.

Conflict of interests:
The authors would like to declare that M.I.M.C. worked for Savana Manager® until March 2022. The rest of the authors have no conflicts of interest to declare.

Note:
M.I.M.C. and A.M.D.M. contributed equally to this work.

How to cite this article:
Morales-Casado MI, Diezma-Martín AM, Muñoz-Escudero F, Rosenstone-Calvo S, Mondéjar-Marín B, Vadillo-Bermejo A, et al. Association between myasthenia gravis and Alzheimer's disease. Rev Neurol 2024; 78: 41-6. doi: 10.33588/rn.7802.2023120.

Versión española disponible en neurologia.com

Introduction

Myasthenia gravis (MG) is an autoimmune disorder [1] in which antibodies are formed against receptors of the neuromuscular junction. Is one of the most common diseases that affects the neuromuscular union. In up to 80% of patients, these antibodies are directed against the acetylcholine receptor [2]. Latest studies indicate a prevalence of some 35,47 × 10^5 habitants. The group over 65 years old represents 62,75% of cases [3].

Classically, MG has been considered a disease with purely motor manifestations, however in the last decades, non-motor symptoms such as cognitive, sleep rhythm and autonomic, have been documented [4]. In the treatment of this pathology, it is used pyridostigmine and immunosuppressive drugs like glucocorticoids or azathioprine [5].

Alzheimer's disease (AD) is considered the first cause of degenerative dementia [6]. Its prevalence increments with age. According to recent estimations, in Spain, the prevalence affects around 3-4% of the population between the ages of 75-79 years, reaching up to 7-34% of the population in those over the age of 85 years [7].

The pathophysiology of AD is characterized by the presence of extracellular neurotic plaques formed by β-amyloid proteins and intracellular neurofibrillary accumulations of the tau protein [8]. This conditions a loss of the cholinergic innervation of the cerebral [9].

Both diseases compromise ACh function. In MG, the dysfunction involving this neurotransmitter occurs at the level of the neuromuscular junction due to autoimmune disorder, whereas in AD, it occurs in central nervous system due to neurodegeneration. There are not studies that clearly demonstrate the alteration of this neurotransmitter in central nervous system in MG patients [10]. Nowadays there are some studies concerning the central nervous system cholinergic involvement in MG physiopathology. One of them supports that nico-

tinic AChRs are not only found in the peripheral nervous system, but are also densely expressed in central nervous system regions such as found in the central nervous system, as well as in the peripheral nervous system, particularly in the hippocampus, hypothalamus, midbrain and cerebral cortex.

Therefore, disrupted cholinergic neurotransmission in the CNS could be related to the manifestations at the cognitive level that are seen in MG. Recent studies indicate that patients with MG may present cognitive problems more frequently than the general population. However, none discriminates between etiologies of cognitive impairment in these patients, and no studies have addressed these alterations in AD [11]. Up until now, there are no studies that report at the possible relation that MG may have with AD. We analyze the possible relation between both diseases.

Patients and methods

The objective of this study was to analyze the possible relation between AD y MG. A multicenter, retrospective, observational study was performed using data obtained by the electronic medical records of patients in the health care system of Castilla-La Mancha (Spain). A system of artificial intelligence was used, which was capable of rephrasing the information in a natural language from the clinical notes. The information that was written by the physicians in the electronic health records during their daily consultations, generated a great amount of very valuable information. Savana Manager® (an artificial intelligence software) maximized a great amount of information found within the electronic health records, based on the dynamic explotation in real time of all the information in the electronic medical records. This program also permitted an immediate descriptive analysis of all the patients included in the platform and offered relevant results along with the variables offered by the user.

Aided by this technology, we were able to obtain clinical data from a total of 3,181,485 patients during January 1, 2011 to May 10, 2020. It has been filtered on the Savana Manager® platform by terms 'Alzheimer's disease' within which the system includes 'Alzheimer's disease', 'Alzheimer' and 'Alzheimer's dementia' and by term 'myasthenia gravis' that platform includes 'Erb-Goldflam disease' and 'myasthenia gravis', including cases of generalized or localized MG (Figure). We have only included cognitive impairment for AD, other types of cognitive impairment were excluded.

To avoid biases due to the difference in age and create comparable groups, we included only patients over the age of 60 years (970,503 patients; no significance difference in age between patients with and without MG; $p > 0,05$). In this subgroup, patients with MG have been identified, and in particular patients with a diagnosis of AD. We have compared the prevalence of this dementia in patients with and without MG (Figure).

We have studied the most important risk factors associated with EA such as hypertension, diabetes mellitus, and dyslipidemia in the both subgroups.

The study abides to legislation and legal requirements keeping in mind what is described in the International Conference on Harmonisation Guide of Proper Medical Practice and the latest edition of the Declaration of Helsinki. We did not have the need to solicit informed consent from each patient included in the study as this study was an observational, retrospective study using anonymous patients.

Statistical analysis

The prevalence of AD in the subgroups of patients (with and without MG) was described in percentages. We used χ^2 analysis in order to compare the prevalence of AD in the two groups along with *odds ratio* and 95% confidence interval, to define the strength and precision of the association.

We used the Z test in order to analyze the possible association among the two groups regarding the risk factors known in AD (sex, cardiovascular risk factors and smoking). Values of $p < 0,05$ were considered statistically significant.

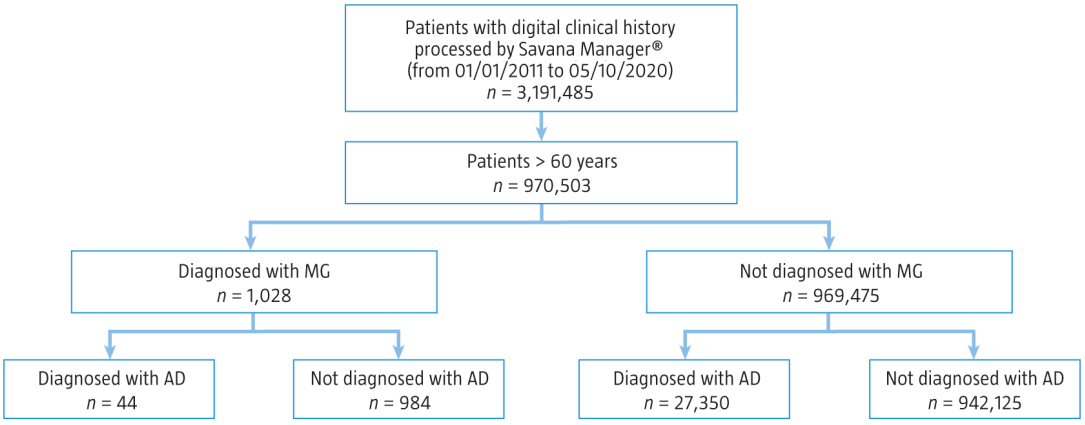
Results

We included an analysis of a total of 970,503 patients age 60 years or older who were seen in the healthcare area of Castilla La-Mancha (Spain) from January 1, 2011 to May 10, 2020. Of these patients, 1,208 patients were diagnosed with MG. a total of 44 patients were also diagnosed with AD (4,28%) (Figure), with an average age of 79,3 years (Confidence interval at 95%: 77,1-81,3) (Figure).

In patients over the age of 60 years without MG (969.475 patients), 27,350 also presented with a diagnosis of AD (2,82%) (Figure) with an average age of 81,1 years (confidence interval at 95%: 81.7-81.9).

From the previous data mentioned, we observed an increase in the prevalence of AD in the group diagnosed previously with MG in comparison to

Figure. Flow chart of patients. AD: Alzheimer's disease; MG: myasthenia gravis.



the general population (4,28% vs. 2,82%), with a significant statistical difference among the two populations ($\chi^{2:}$ 7,96; p = 0,0047) and an *odds ratio* of 1,54 (Confidence interval at 95%: 1,13-2,08; p = 0,0051).

The demographic characteristics of the population sample is described in the table. There were no significant statistical differences between the groups with and without MG when comparing the primary risk factors described in AD such as cardiovascular risk and smoking habit. These results minimized the possibility that the differences observed in the prevalence of AD could cause these risk factors to be confounding variables (Table).

We have analyzed the specific treatment of AD with acetylcholinesterase inhibitors. The drugs of this type most frequently administered, was rivastigmine and donepezil, without significant statistical difference among them both in patents with MG as in the general population.

Discussion

MG and AD are two of the most important neurological diseases with compromised ACh function. In MG, the dysfunction involving this neurotransmitter occurs at the level of the neuromuscular junction, whereas in AD, it occurs in central nervous system [12,13]. Our study demonstrates an increase in AD prevalence in patients previously diagnosed with MG, without statistically significant difference in important risk factors of AD such as age, gender, hypertension, hyperlipidemia, diabetes type 2 [14].

The association between MG and AD does not demonstrate causality, future studies would provide valuable insights size to confirm this causality. These future investigations should take into account on the criteria of Bradford Hill [15].

In our study we have considered the modifiable lifestyle factors (hypertension, hyperlipidemia, diabetes type 2, obesity, smoking) [16]. Available evidence suggests vascular risk factors play a critical role in the development of cognitive decline and AD. In fact, it could even constitute an independent risk factor for dementia, contributing to the development of AD. Preventing risk factors could be achieved in order to prevent or delay the deterioration of cognitive functions in patients with AD [16]. However, we did adjust for risk factors in both groups. There were no significant statistical differences between the groups with and without MG when comparing this risk factors. These results minimized the possibility that the differences observed in the prevalence of AD could cause these risk factors to be confounding variables. Therefore, there is a much stronger argument for considering in the relationship between them MG as an independent risk factor for AD.

We propose some hypothesis concerning the mechanisms underlying the association between MG and AD. One of them supports a direct relationship between both diseases. In this direction studies support patients with MG may present cognitive problems more frequently than the gen-

Table. Description of the sample of patients with Alzheimer's disease.

	With MG (*n* = 44)	Without MG (*n* = 27350)	Z test	*p*
Age	79.3 years CI 95%: 77.1-81.3	81.8 years CI 95%: 81.7-81.9		
Female	61.3%	65.81%	0.6	0.529
HTN	79.55%	71.3%	1.2	0.22
DM	34.09%	35.09%	0.1	0.88
DLP	56.82%	45.9%	1.5	0.14
Tobacco	9.09%	7.59%	0.1	0.6545

CI: confidence interval; DLP: dyslipidemia; DM: diabetes mellitus; HTN: hypertension; MG: myasthenia gravis.

eral population [17]. This could be related to the fact that the nicotinic AChRs are not only found in the peripheral nervous system, but are also expressed in CNS [11]. However, none discriminates between etiologies of cognitive impairment in these patients, and no studies have addressed these alterations in AD. Indeed, studies of the cognitive performance of MG patients concluded that decrease central cholinergic activity produced higher cognitive dysfunction [10]. Therefore, disrupted cholinergic neurotransmission in the CNS could be related to the association between MG and AD. On the other hand, there are also studies that do not show an increased risk of AD in patients with MG [18].

In another direction, previous reports suggest that patients with autoimmune diseases, like psoriasis, may present cognitive decline more frequently than the general population [19]. In this regard, evidence indicates autoimmune diseases may be associated with a higher risk of AD [16, 20,21].

Other alternative explanations have emerged for memory impairments in patients with MG. The physical and mental weakness, as well as depression, associated to chronic diseases, like MG, could cause cognitive deficits [22]. On this way there is evidence that glucocorticoid treatment may lead to disturbance of cognitive functions [23]. Evidence suggests that long-term glucocorticoid exposure may cause cognitive impairment [24].

Previous results evidenced chronic corticosterone consumption anticipated the induction of the Aβ pathology. Other study shows correlation between corticoid consumption and higher risk to develop AD [25].

All these hypotheses are speculative and require further investigation to be elucidated.

Our study only shows the association between both pathologies without being able to elucidate the cause. The psychosocial and cognitive aspects of MG represent an emerging area of research and clinical interest.

The increase of the prevalence of AD in the elderly population has been documented. Epidemiological studies show increased prevalence of MG in the elderly population.

Latest studies indicate a prevalence of 260 x10^6 habitants. In the over 60 years age group the prevalence reached 518 cases per million inhabitants [5]. In other works, these findings also highlight, it shows a prevalence of 1.224 per million inhabitants in this group [3]. In our study only we only analyzed the population over 60 years of age. The finding of an increased prevalence of AD and MG in our sample could be related with its aging. In this regard, further investigations are needed to know the cognitive situation in patients with early-onset MG (under 50 years old) and their progression.

Another important aspect of such relation could be the ability to reach more profoundly the pathophysiology of AD. It could open new possibilities to develop new therapeutic targets, given that no drug cures AD disease.

Taking into consideration the association between AD and MG, control of cardiovascular risk could delay the beginning of AD in these patients. Recent works have shown the effects of cognitive interventions for people with dementia. Cognitive interventions can improve or maintain cognitive function in these patients [26]. Cognitive stimulation could be applied as a prevention strategy in patients with MG too. Thus, intervention on modifiable risk factors for AD and cognitive stimulation as primary prevention could constitute effective measures as prevention for MG patients [27,28]. It could be considered as a complementary intervention option.

This study has some limitations that deserve to be mentioned. Firstly, our study is an observational, retrospective study with data from electronic health records and coded by the Savana Manager® software. It is possible the results of some of the variables could be altered by the type of information collected and the quality of the information available in the patient histories, with previously established diagnoses. These factors may cause a bias when collecting data, for example we have not been

able to consider variables such as fatigue or depression. It would be interesting to propose new epidemiological studies taking these variables into account.

Conclusion

In conclusion, our study showed a significant increase in the prevalence of AD in patients previously diagnosed with MG over the age of 60 years not related to other known risk factors, suggesting that MG is an independent risk factor. This association does not demonstrate causality, but this opens the possibility of a potential pathophysiological relationship between both diseases. Keeping in mind that both pathologies share a dysregulation in Ach neurotransmission, it is here where the paths between them may cross. However, the weight of autoimmunity in this relationship should not be overlooked. Future prospective studies with a larger sample would provide valuable insights size to confirm these findings.

References

1. García-Estévez DA, Fraga-Bau A, García-Sobrino T, Mederer-Hengstl S, Pardo-Fernández J. Epidemiología de la miastenia grave en la península ibérica y Latinoamérica. Rev Neurol 2023; 76: 59-68.
2. Lindstrom JM, Seybold ME, Lennon VA, Whittingham S, Duane DD. Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value. Neurology 1976; 26: 1054-9.
3. Aragonès JM, Altimiras J, Roura P, Alonso F, Bufill E, Munmany A, et al. Prevalencia de miastenia gravis en la comarca de Osona (Barcelona, Cataluña). Neurologia 2017; 32: 1-5.
4. Zhou X, Cao S, Hou J, Gui T, Zhu F, Xue Q. Association between myasthenia gravis and cognitive disorders: a PRISMA-compliant meta-analysis. Int J Neurosci 2023; 133: 987-98.
5. García-Estévez DA, López-Díaz LM, Pardo-Parrado M, Pérez-Lorenzo G, Sabbagh-Casado NA, Ozaita-Arteche G, et al. Epidemiología de la miastenia gravis en la provincia de Ourense (Galicia, noroeste de España). Neurologia 2023; 38: 75-81.
6. Villarejo-Galende A, Eimil-Ortiz M, Llamas-Velasco S, Llanero-Luque M, López-de Silanes de Miguel C, Prieto-Jurczynska C. Report by the Spanish Foundation of the Brain on the social impact of Alzheimer disease and other types of dementia. Neurologia (Engl Ed) 2021; 36: 39-49.
7. Takizawa C, Thompson PL, van Walsem A, Faure C, Maier WC. Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. J Alzheimers Dis 2015; 43: 1271-84.
8. Gulisano W, Maugeri D, Baltrons MA, Fà M, Amato A, Palmeri A, et al. Role of Amyloid-β and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade. J Alzheimers Dis 2018; 64 (Suppl 1): S611-31.
9. Aubert I, Araujo DM, Cécyre D, Robitaille Y, Gauthier S, Quirion R. Comparative alterations of nicotinic and muscarinic binding sites in Alzheimer's and Parkinson's diseases. J Neurochem 1992; 58: 529-41.
10. Kaltsatou A, Fotiou D, Tsiptsios D, Orologas A. Cognitive impairment as a central cholinergic deficit in patients with Myasthenia Gravis. BBA Clin 2015; 3: 299-303.
11. Tucker DM, Roeltgen DP, Wann PD, Wertheimer RI. Memory dysfunction in myasthenia gravis: evidence for central cholinergic effects. Neurology 1988; 38: 1173-7.
12. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol 2018; 25: 59-70.
13. Aguirre F, Fernández RN, Arrejoría RM, Manin A, Cores VE, Sivori M, et al. Peak expiratory flow and the single-breath counting test as markers of respiratory function in patients with myasthenia gravis. Neurologia (Engl Ed) 2023; 38: 405-11.
14. Serrano-Pozo A, Growdon JH. Is Alzheimer's disease risk modifiable? J Alzheimer Dis 2019; 67: 795-819.
15. Höfler M. The Bradford Hill considerations on causality: a counterfactual perspective. Emerg Themes Epidemiol 2005; 2: 11.
16. De la Torre JC. Vascular risk factor detection and control may prevent Alzheimer's disease. Ageing Res Rev 2010; 9: 218-25.
17. Ayres A, Winckler PB, Jacinto-Scudeiro LA, Rech RS, Jotz GP, Olchik MR. Cognitive performance in patients with myasthenia gravis: an association with glucocorticosteroid use and depression. Dement Neuropsychol 2020; 14: 315-23.
18. Wotton CJ, Goldacre MJ. Associations between specific autoimmune diseases and subsequent dementia: retrospective record-linkage cohort study, UK. J Epidemiol Community Health 2017; 71: 576-83.
19. Sitek EJ, Bilińska MM, Wieczorek D, Nyka WM. Neuropsychological assessment in myasthenia gravis. Neurol Sci 2009; 30: 9-14.
20. Brunner R, Schaefer D, Hess K, Parzer P, Resch F, Schwab S. Effect of corticosteroids on short-term and long-term memory. Neurology 2005; 64: 335-7.
21. Coluccia D, Wolf OT, Kollias S, Roozendaal B, Forster A, de Quervain DJF. Glucocorticoid Therapy-induced memory deficits: acute versus chronic effects. J Neurosci 2008; 28: 3474-8.
22. Canet G, Zussy C, Hernandez C, Chevallier N, Marchi N, Desrumaux C, et al. Chronic glucocorticoids consumption triggers and worsens experimental Alzheimer's disease-like pathology by detrimental immune modulations. Neuroendocrinology 2022; 112: 982-97.
23. Pankowski D, Wytrychiewicz-Pankowska K, Owczarek W. Cognitive impairment in psoriasis patients: a systematic review of case-control studies. J Neurol 2022; 269: 6269-78.
24. Li X, Sundquist J, Zöller B, Sundquist K. Dementia and Alzheimer's disease risks in patients with autoimmune disorders. Geriatr Gerontol Int 2018; 18: 1350-5.
25. Yeung CHC, Au Yeung SL, Schooling CM. Association of autoimmune diseases with Alzheimer's disease: a mendelian randomization study. J Psychiatr Res 2022; 155: 550-8.
26. Wang YY, Yang L, Zhang J, Zeng XT, Wang Y, Jin YH. The effect of cognitive intervention on cognitive function in older adults with Alzheimer's disease: a systematic review and meta-analysis. Neuropsychol Rev 2022; 32: 247-73.
27. Litke R, Garcharna LC, Jiwani S, Neugroschl J. Modifiable risk factors in Alzheimer disease and related dementias: a review. Clin Ther 2021; 43: 953-65.
28. Maliszewska-Cyna E, Lynch M, Oore JJ, Nagy PM, Aubert I. The benefits of exercise and metabolic interventions for the prevention and early treatment of Alzheimer's disease. Curr Alzheimer Res 2017; 14: 47-60.

Miastenia *gravis* y enfermedad de Alzheimer: una asociación a estudio

Introducción. La miastenia *gravis* (MG) y la enfermedad de Alzheimer (EA) son dos de las enfermedades neurológicas en cuya fisiopatología interviene la acetilcolina en distintos niveles. En la primera, la alteración de este neurotransmisor se produce en la unión neuromuscular, y en la segunda, en el sistema nervioso central.

Objetivo. Analizar la posible relación entre dichas patologías estudiando la prevalencia y la *odds ratio* de la EA dentro de los pacientes diagnosticados de MG con respecto a la prevalencia de EA en la población general.

Pacientes y métodos. Se han examinado datos de las historias clínicas electrónicas del sistema de salud de Castilla-La Mancha utilizando el procesamiento de lenguaje natural a través de la plataforma clínica de inteligencia artificial Savana Manager®.

Resultados. Se ha identificado a 970.503 pacientes mayores de 60 años, de los que 1.028 tenían diagnóstico de MG. La proporción de pacientes con diagnóstico de EA dentro de este grupo (4,28%) es mayor que en el resto de la población (2,82%; p = 0,0047), con una *odds ratio* de 1,54 (intervalo de confianza al 95%: 1,13-2,08; p = 0,0051), sin que se encuentren diferencias significativas en el análisis bivariante del resto de los factores de riesgo para EA más importantes conocidos hasta ahora.

Conclusiones. Nuestros resultados sugieren que podría existir un aumento de la prevalencia de EA en pacientes con MG.

Palabras clave. Acetilcolina. Alteraciones cognitivas. Demencia de tipo Alzheimer. Enfermedad de Alzheimer. Memoria. Miastenia *gravis.*