Arq Neuropsiquiatr 2002;60(3-A):519-524

# MYASTHENIC CRISIS

## Report of 24 cases

*Lineu Cesar Werneck, Rosana Herminia Scola, Francisco Manoel Branco Germiniani, Enio A. Comerlato, Francisco Marcos Bezerra Cunha*

ABSTRACT - Myasthenic crisis (MC) is a life-threatening complication of myasthenia gravis (MG) with a high mortality rate. The aim of our study was to review the different therapeutics approaches in the treatment of MC and their impact in the final outcome. We reviewed the medical files of patients diagnosed with MG admitted between February 1993 and October 1997, who developed MC. Sex, mean age, disease's duration, functional scale, symptoms preceding the crisis, crisis therapy in each set and mortality were then analysed. There were 24 patients who developed MC, 21 females and 3 males, with 1 neonatal, 1 congenital sporadic, 17 juvenile/adult, 3 over 50 years and 2 with thymoma. Dysphagia, dysphonia and dysartria were the most common symptoms preceding the crisis. A precipitating factor was elicited in 8 cases and the most common was infection (upper airway infection, urinary tract infection and pneumonia). 16 patients needed a nasogastric tube and 9 had a tracheostomy performed. 24 patients used anticholinesterase drugs, 21 prednisone, 7 immunosuppressive agents, 5 plasmapheresis, 3 human hyperimune gamma immunoglobulin and 12 had thymectomy. A good response was obtained in 13, satisfactory in 7 and there were 4 deaths. We concluded that in spite of all the therapeutics options, there were non statistically significant differences in the outcome of patients that underwent thymectomy and those who did not.

KEY WORDS: myasthenia gravis, myasthenic crisis, thymectomy, neuromuscular disorders, muscle diseases.

**Crise miastênica: relato de 24 casos**

RESUMO - A crise miastênica (CM) é uma complicação preocupante da miastenia grave (MG) que apresenta altos índices de mortalidade. Neste estudo revisamos as diferentes abordagens no tratamento da CM e seu impacto no resultado final. Levantamos os dados dos pacientes com MG que desenvolveram CM admitidos entre fevereiro de 1993 e outubro de 1997. Foram analisados as interrelações do sexo, idade media, duração da doença, escala funcional, sintomas e procedimentos precedendo as crises, terapêutica empregada e mortalidade. Foram encontrados 24 casos que desenvolveram CM, sendo 21 do sexo feminino e 3 do masculino. Em relação à apresentação clínica, 1 era da forma neonatal, 1 congênita esporádica, 17 juvenil/adulta, 3 acima de 50 anos e 2 com timoma. Os sintomas principais que precederam a CM foram disfagia, disfonia e disartria. Foi possível identificar um fator desencadeante em 8 casos e o mais comum foi infecção (vias aéreas, pneumonia e trato urinário). Necessitaram de sonda nasogastrica 16 casos e a traqueostomia, 9. Usaram medicações anticolinesterásicas todos os 24 casos, prednisona 21, imunossupressivos 7, plasmaferese 5, gamaglobulina hiperimune 3 e foram submetidos a timectomia 12 casos antes ou após a CM. Obtivemos bom resultado em 13, satisfatório em 7 e ocorreram 4 óbitos, sendo 3 não relacionados com a CM. Concluímos que apesar das várias opções terapêuticas empregadas, não houve diferença estatística entre os pacientes submetidos a timectomia e os com tratamento conservador.

PALAVRAS-CHAVE: miastenia grave, crise miastênica, timectomia, doenças neuromusculares, miopatias.

Myasthenia gravis (MG) is an autoimmune disease that compromises the neuromuscular junction as a result of the activity of anti-acetylcholine receptor antibodies (anti-AchR) on the post-synaptic membrane, leading to symptoms of fatigue and decreased muscle strength[1-4]. MG is a rare disease with a prevalence of 0.5 to 5 cases per 100,000 habitants and an incidence of 0.4 cases per 100,000. In Brazil there are probably 15,500 persons affected by the disease[5].

The main complication of MG is the myasthenic crisis (MC), which is characterised by a fast, markedly decrease of muscle strength and compromise

Neuromuscular Diseases Unit, Neurology Division, Internal Medicine Department, Hospital de Clínicas da Universidade Federal do Paraná (UFPR), Curitiba PR, Brazil.

Received 23 October 2001, received in final form 1 February 2002. Accepted 13 February 2002.

*Dr. Lineu Cesar Werneck - Serviço de Neurologia, Hospital de Clínicas,UFPR - Rua General Carneiro 181, 12 andar - 80080-900 Curitiba PR, Brasil.*

of bulbar muscles with dysphonia, dysphagia and aspiration. If not treated, the weakness progresses compromising respiratory muscles, leading to respiratory insufficiency and, ultimately, death[1,3,6-8]. The death rate of MC has drastically decreased after the fifties, from 80% to less than 10%, thanks to the use of early mechanical ventilation, admission of the myasthenic patient to an Intensive Care Unit (ICU), recognition and treatment of precipitating factors, edrophonium testing, use of anticholinesterase drugs, steroid therapy, immunosuppression, plasmapheresis and IV human gamma globulin[1,3,6].

The objective of our study was to review the clinical features of the myasthenic patients who developed MC.

## METHOD

We reviewed the medical files of all the patients admitted to the Hospital de Clínicas da Universidade Federal do Paraná – Curitiba, Brazil, as well of patients referred from one of the author's own clinic, with a diagnosis of MG from February 1973 to October 1997. Of all the 188 myasthenic patients studied, 24 had MC.

The patients were grouped according to their clinical features in the following groups: neonatal, congenital sporadic, ocular, juvenile/adult, over 50 years old and with thymoma. Detailed criteria for grouping myasthenic patients in different categories has already been published and can be found elsewhere[1,2,7]. We then analysed in each group the gender distribution, mean age at MC, duration of the disease, precipitating factors, therapeutic approach, mortality, symptoms prior to MC and functional status.

The Osserman's scale was used at diagnosis and a functional scale (remission, controlled, compensated, partially controlled, no response and death) scale[7] was used at diagnosis, during MC, at hospital discharge and at the final evaluation, 6 months later, in each group.

The patients who underwent thymectomy were evaluated using the functional scale during MC and after 6 months and the results were compared with those of the patients who did not undergo thymectomy.

## RESULTS

Among our 188 patients with MG, 24 had a MC, mainly in the juvenile/adult group, followed in decreasing order by thymomatous, congenital, neonatal and over 50 years groups. There were 4 deaths – 16.7% of all MC cases (Table 1).

Three men only had MC, whereas 21 female patients developed MC. All the male patients had thymomatous MG. The mean age at MC was 24 (range: 13–56) in the juvenile/adult group and 39.5 years in the thymomatous subgroup (range: 19–76). The mean time of disease when the patients developed MC was 4.11 years (Table 1).

On initial evaluation, before developing a MC, the majority of patients could be classified as Osserman's group III, followed by groups IIA and IIB. Overall, 96% (n=23) of our patients had generalised MG (Table 1).

Functional evaluation was based on a functional scale. On first evaluation, most patients were partially controlled in the juvenile/adult group, and 5 patients were diagnosed when they presented with MC (Table 2).

During MC, most of the patients were of the juvenile/adult type and had either a poorly controlled or with no functional response (Table 2). Dysphagia, dysphonia and dysartria preceded the MC one or two weeks and could be found in all patients.

At hospital discharge the majority of patients

*Table 1. Types of myasthenia gravis related to mortality, sex, age, duration of disease, and Osserman's scale.*

| | Neonatal | Congenital | Juvenile/Adult | > 50 years | Thymoma | Total |
|---|---|---|---|---|---|---|
| Mortality | | | | | | |
| Number of crisis | 1 (4%) | 1 (4%) | 16 (68%) | 1 (4%) | 5 (20%) | 24 (100%) |
| Deaths | - | - | 1 | 1 | 2 | 4 (16.7%) |
| Sex | | | | | | |
| Female | 1 | 1 | 16 | 1 | 2 | 21 |
| Male | - | - | - | - | 3 | 3 |
| Mean age (years) | 0.01 | 4 | 24 | 69 | 39.5 | |
| Duration of disease (years) | 0.01 | 0.64 | 4.11 | 3.25 | 1.52 | |
| Osserman's Scale | | | | | | |
| I | - | 1 | - | - | - | 1 |
| II A | 1 | - | 5 | - | - | 6 |
| II B | - | - | 4 | 1 | - | 5 |
| III | - | - | 5 | - | 5 | 10 |
| IV | - | - | 1 | - | - | 1 |

*Table 2. Functional evaluation and type of myasthenia gravis.*

| | Neonatal | Congenital | Juvenile/ Adult | > 50 years | Thymoma | Total |
|---|---|---|---|---|---|---|
| First evaluation | | | | | | |
| Controlled | - | - | 3 | - | 1 | 3 (12.5) |
| Compensated | 1 | 1 | 3 | - | 1 | 6 (25) |
| Partially Controlled | - | - | 9 | 1 | 1 | 11 (45.8) |
| No response | - | - | 1 | - | 3 | 4 (16.7) |
| During MC | | | | | | |
| Partially Controlled | 1 | 1 | 1 | - | - | 3 (12.5) |
| Poorly Controlled | - | - | 4 | - | 1 | 5 (20.8) |
| No Response | - | - | 11 | 1 | 4 | 16 (66.7) |
| At hospital discharge | | | | | | |
| Controlled | 1 | - | 1 | - | 4 | 6 (25) |
| Partially Controlled | - | 1 | 10 | - | - | 11 (45.8) |
| Poorly Controlled | - | - | 4 | - | - | 4 (16.7) |
| Death | - | - | - | 1 | 2 | 3 (12.5) |
| Final functional evaluation | | | | | | |
| Remission | - | - | 1 | - | 1 | 2 (8) |
| Controlled | 1 | - | 9 | - | 2 | 12 (50) |
| Partially Controlled | - | 1 | 5 | - | - | 6 (25) |
| Death | - | - | 1 | 1 | 2 | 4 (16.7) |

*Table 3. Precipitating factors.*

| Type of myasthenia | Infection | Iodinated contrast | Puerperium | Emotional factors | Unknown |
|---|---|---|---|---|---|
| Neonatal | - | - | - | - | 1 |
| Congenital | - | - | - | - | 1 |
| Juvenile/Adult | 5 | 1 | 2 | 1 | 7 |
| > 50 years | - | - | - | - | 1 |
| Thymoma | 1 | - | - | - | 4 |
| Total | 6 (25%) | 1 (4%) | 2 (8%) | 1 (4%) | 14 (69%) |

(n=17) were either controlled or partially controlled, with a few (n=4) remaining in the poorly controlled group. There were 3 deaths during MC, but two of them were not directly related to MC. One patient died during MC as a result of pulmonary thromboembolism, another due to a cardiac arrhythmia, one died at home and his death was not related to MC. Only one patient died due to MC. These results are summarized in Table 2.

All the patients who developed MC were followed for at least 6 months and at the final evaluation most of them were either controlled or in remission. Only one patient, in addition to the three patients who died while in ICU, died suddenly at home due to respiratory insufficiency months after the discharge (Table 2).

A precipitating factor could not be elicited in 69% (n=14). However, when a direct cause for the crisis could be elicited from either the history or physical examination the most common precipitating factor was infection (upper airway infection, urinary tract infection and pneumonia) affecting 6 (25%) patients. Other precipitating factors were puerperium in 2 patients, emotional factors in one patient and previous exposure to iodinated contrast in only one patient. With the progression of the disease, almost all patients who needed mechanical ventilatory support had an underlying pneumonia, which can be considered a risk factor for prolonged intubation in MC (Table 3).

All our patients were treated with anticholinesterase drugs. All but one received prednisone. As for other therapeutical options such as plasma exchange

*Table 4. Therapeutical measures.*

| | Neonatal | Congenital | Juvenile/ Adult | > 50 years | Thymoma | Total |
|---|---|---|---|---|---|---|
| *Specific treatment* | | | | | | |
| Anticholinesterase drugs | 1 | 1 | 16 | 1 | 5 | 24 (100%) |
| Prednisone | - | 1 | 16 | - | 5 | 23 (95.8%) |
| Plasma exchange | - | - | 3 | - | 1 | 4 (16.6%) |
| Immunoglobulin | - | - | 4 | - | - | 4 (16.6%) |
| Thymectomy | | | | | | |
| Prior to MC | - | - | 6 | 1 | 3 | 10 (41.4%) |
| During MC | - | - | 3 | - | 1 | 4 (16.6%) |
| After MC | - | - | 1 | - | 1 | 2 (10%) |
| Total | - | - | 10 | 1 | 5 | 16 (68%) |
| *Supportive measures* | | | | | | |
| Nasogastric tube | - | - | 13 | - | 4 | 17 (70.8%) |
| Mechanical ventilation | - | - | 10 | - | 3 | 13 (54.2%) |
| Tracheostomy | - | - | 6 | - | 2 | 8 (33.3%) |

and immunoglobulin, the same number of patients (4 in each group) received either treatment. The therapeutic measures used in the treatment of MC in our series, including thymectomy, are shown in Table 4.

A worsening of symptoms prompted the need of a nasogastric tube, mechanical ventilation and tracheostomy as supportive measures in 17, 13 and 8 patients respectively. (Table 4).

Ten patients had already undergone thymectomy before MC, 4 underwent it while in MC and 2 after recovery from MC, with a total number of 16 thymectomies performed (Table 5).

Thymectomy had no statistical relevance in either the natural history of the MC or the final outcome. On final evaluation, most of the patients had their symptoms controlled (Table 2).

## DISCUSSION

Myasthenic crisis is a medical emergency defined by respiratory failure requiring mechanical ventilation, occurring in 15-20% of MG patients[6]. Among our patients the incidence of MC was 12.76% and it was more frequent in the first 2 years of disease. These numbers are similar to those of another series with 44 patients, where the average time between the initial symptoms of MG and MC was of 37 months. In that study, the female/male ratio was roughly 1.5:1[3]. The majority of our patients who developed MC were female, results similar to those of the Columbia-Presbiterian series[6].

The precipitants of MC include, among others, infections, exposure to toxic substances, emotional factors, surgery, thyroid diseases and the use of some medications (aminoglicosides, tetracycline, sulphonamides, polimixine, lincomicine, phenitoin, carbamazepine, quinidine, verapamil, propranolol, procaninamide, lidocaine, muscle relaxing agents, cloroquine, quinine, lithium, chlorpromazine, diazepam, opioids, barbiturates, corticosteroids, thyroxin, triiodotironine, magnesium salts, metroclopramide). A precipitating factor could not be elicited in most of our cases. Whenever a precipitating factor can be elicited, infections are the leading cause of MC as noted in several studies[3,6,10]. In the Columbia-Presbiterian series infection was the precipitant of MC in as many as 38% of patients.

As for the cases of MC in the puerperium, the abrupt fall of alpha-fetoprotein (AFP) serum levels[11,12], which tend to be high due to its production during pregnancy, could be a trigger factor for MC, possibly due cessation of inhibition the binding of anti-AchR at the neuromuscular junction.

There were also cases of MC following the intravenous injection of iodinated contrast[13,14]. How contrast material can precipitate MC is still uncertain, but precaution and the use of safety measures when submitting a myasthenic patient to contrast enhanced imaging methods, as in the investigation for a thymoma, cannot be over emphasised.

Prompt treatment of MC leads to clinical improvement and can be life-saving. The main treatment measures for the treatment of MC are: admission to an ICU with ventilatory support, suspension of anticholinesterase drugs in the first 48-72 hours of treatment, antibiotic treatment of underlying infections, plasmapheresis, intravenous gamma immunoglobu-

*Table 5. Thymectomized x non thymectomized patients, functional scale on initial and final evaluation.*

| | Thymectomy | | Conservative treatment | |
|---|---|---|---|---|
| Functional scale | Initial evaluation | Final evaluation | Initial evaluation | Final evaluation |
| Remission | - | 1 (6,25%) | - | - |
| Controlled | 2 (12.5%) | 8 (50%) | 1 (12.5%) | 5 (62.5%) |
| Compensated | 2 (12.5%) | | 4 (50%) | |
| Partially Controlled | 8 (50%) | 3 (18,25%) | 3 (37.5%) | 3 (37.5%) |
| No Response | 4 (25%) | - | | |
| Deaths | - | 4 (25%) | | |

lin and oral corticosteroids[1,3,6,8,9]. In selected cases edrophonium testing might prove helpful. A worsening of symptoms prompted the need of a nasogastric tube, mechanical ventilation and tracheostomy as supportive measures in 17, 13 and 8 patients respectively. These measures are one of the cornerstones of MC treatment as they improve the ventilatory function of the critically ill patients[1,3,6,8,10]. Weaning of ventilator support was based on both clinical improvement and gasometric parameters, as in any critically ill patient.

There is no consensus in the medical literature concerning the use of anticholinesterase drugs during MC, with several studies suggesting that the use of these drugs should be arrested for 48 up to 72 hours, so that the postsynaptic membrane might "rest", allowing for expression of new acetylcholine receptors on the motor end plate, and later reintroduced by nasogastric tube[1,3,6,9,15].

Corticotherapy is warranted by several authors[3,6], even though some suggest pulse therapy[1] rather than oral corticotherapy.

As for other therapeutical options such as plasma exchange and immunoglobulin, the same number of patients (4 in each group) received either treatment. Plasmapheresis is indicated for myasthenic patients in crisis as it lowers the complication rate of MC and shortens its duration, with clinical response occurring within days[1,3,8,9]. It can also be used prior to thymectomy, as it reduces the levels of circulating antibodies against acethilcoline receptors[1,8,10]. Some groups use plasmapheresis in as many as 74% of patients with MC[6]. In a study performed in Baltimore, seven patients were treated with plasmapheresis, leading to better outcomes when compared with patients who did not undergo plasma exchange[10]. In another study, the authors found that plasmapheresis might be more effective therapy for MC than immunoglobulin[8].

The role of thymectomy in the natural history of MG is a matter of continuous discussion since its introduction as a treatment option in MG[16-18]. Some series show that of 74 thymectomized patients as many as 34 patients have complete remission of their symptoms and 36 patients had substantial improvement[17]. It seems that thymoma may be a risk factor for MC, as more severe symptoms are found in patients with thymomatous MG[6]. In our series, of all the 24 patients who developed a MC, only five patients (2 females and 3 males) had thymomatous MG. Only one patient in the subgroup with thymoma, as well as 3 patients in the juvenile, non-thymomatous subgroup underwent thymectomy during MC. As for the remainder of the thymomatous subgroup, three patients had thymectomy performed prior to their developing MC and one patient underwent thymectomy after the MC had resolved.

In addition, seven patients with non-thymomatous MG (6 with juvenile/adult MG and one older than 50 years) had already undergone thymectomy before their MC. Another patient with juvenile MG underwent thymectomy after MC. In our study, as well as others[16], there were no statistically significant differences in outcome between the thymectomized and non-thymectomized groups. In the final evaluation all the patients who did not undergo a thymectomy were either partially or fully controlled while 12 thymectomized patients had a similar outcome (Table 5). All the deaths (n=4) occurred among thymectomized patients.

Patients older than 50 were at a higher risk of developing MC, which increased if there was a conco-

mitant thymoma. Elder patients have a higher incidence of cardiac disease, pulmonary thromboembolism, acute renal failure and hospital-acquired pneumonia among other complicating factors during MC, thus increasing the death rate in such cases.

At hospital discharge the majority of our patients were either controlled or partially controlled, with a few remaining in the poorly controlled group. There were 3 deaths during MC, but two of them were not directly related to MC. These results are similar to those found by other authors[3].

In conclusion, despite all other therapeutical options, there were non statistically significant differences in the outcome of MC patients who underwent thymectomy and those who did not.

## REFERENCES


1. Oosterhuis HJGH. Myasthenia gravis. Edinburgh: Churchill Livingstone, 1984:2011-2015.
2. Sanders DB. Myasthenia gravis and myasthenic syndromes. Neurologic Clinics of North America 1994;12:243-262.
3. Berrouschot J, Baumann I, Kalischewski P, Strker M, Schneider D. Therapy of myasthenic crisis. Crit Care Med 1997;25:1228-1235.
4. Bonifati DM, Angelinil C. Long-term cyclosporine treatment in a group of severe myasthenia gravis patients. J Neurol 1997;244:542-547.
5. Assis JM. Miastenia grave. São Paulo: Sarvier, 1990:10.
6. Thomas CE, Mayer SA, Gungor Y, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. Neurology 1997;48:1253-1260.
7. Cunha FMB, Scola RH, Werneck LC. Miastenia grave: avaliação clínica de 153 pacientes. Arq Neuropsiquiatr 1999;57:457-464.
8. Stricker RB, Kwiatkowska BJ, Habis JA, Kiprov DD. Myasthenic crisis: response to plasmapheresis following failure of intravenous gamma globulin. Arch Neurol 1993;50:837-840.
9. Saltis LM, Martin BR, Traeger SM, Bonfiglio MF. Continuos infusion of pyridostigmine in the management of myasthenic crisis. Crit Care Med 1993;21:938-940.
10. Sellman MS, Mayer RF. Treatment of myasthenic crisis in late life. South Med J 1985;78:1208-1210.
11. Plauchê WC. Myasthenia gravis in mothers and their newborns. Clin Obstet Gynecol 1991;34:82-99.
12. Hatada Y, Munemura M, Matsuo I, Fujisaki S, Okamura H, Yamanaka N Myasthenic crisis in the puerperium: the possible importance os alpha-fetoprotein: case report. Br J Obstet Gynaecol 1987;94:480-482.
13. Chagnac Y, Hadani M, Goldhammer Y. Myasthenic crisis after intravenous administration of iodinated contras agent. Neurology 1985;35:1219-1220.
14. Hilton-Jones D. Myasthenic crisis precipitated by iodinated contrast agents. Neurology 1986;36:444.
15. Borel CO. Management of myasthenic crisis. Continuous anticholinesterase infusions. Crit Care Med 1993;21:821-822.
16. Werneck LC, Teive HAG. Myasthenia grave: avaliação clínica e terapêutica de 55 casos. Arq Neuropsiquiatr 1987;45;379-390.
17. Huang MH, King KL, Hsu WH, et al. The outcome of thymectomy in non thymomatous myasthenia gravis. Surg Gynecol Obstet 1988;166:436-440.
18. Werneck LC, Cunha FMB, Scola RH. Myasthenia gravis: a retrospective study comparing thymectomy to conservative treatment. Acta Neurol Scand 2000;101:41-46.