ARTICLE

# Myasthenic crisis demanding mechanical ventilation

## A multicenter analysis of 250 cases

Bernhard Neumann, MD, Klemens Angstwurm, MD, Philipp Mergenthaler, MD, Siegfried Kohler, MD, Silvia Schönenberger, MD, Julian Bösel, MD, Ursula Neumann, PhD, Amelie Vidal, Hagen B. Huttner, MD, Stefan T. Gerner, MD, Andrea Thieme, MD, Andreas Steinbrecher, MD, Juliane Dunkel, MD, Christian Roth, MD, Haucke Schneider, MD, Eik Schimmel, MD, Hannah Fuhrer, MD, Christine Fahrendorf, MD, Anke Alberty, MD, Jan Zinke, MD, Andreas Meisel, MD, Christian Dohmen, MD, and Henning R. Stetefeld, MD,* for The German Myasthenic Crisis Study Group

**Correspondence**
Dr. Stetefeld
henning.stetefeld@uk-koeln.de

*Neurology*® 2020;94:e299-e313. doi:10.1212/WNL.0000000000008688

## Abstract

### Objective

To determine demographic characteristics, clinical features, treatment regimens, and outcome of myasthenic crisis (MC) requiring mechanical ventilation (MV).

### Methods

Analysis of patients who presented with MC between 2006 and 2015 in a German multicenter retrospective study.

### Results

We identified 250 cases in 12 participating centers. Median age at crisis was 72 years. Median duration of MV was 12 days. Prolonged ventilation (>15 days) depended on age ($p$ = 0.0001), late-onset myasthenia gravis (MG), a high Myasthenia Gravis Foundation of America Class before crisis ($p$ = 0.0001 for IVb, odds ratio [OR] = infinite), number of comorbidities (>3 comorbidities: $p$ = 0.002, OR 2.99), pneumonia ($p$ = 0.0001, OR 3.13), and resuscitation ($p$ = 0.0008, OR 9.15). MV at discharge from hospital was necessary in 20.5% of survivors. Patients with early-onset MG ($p$ = 0.0001, OR 0.21), thymus hyperplasia ($p$ = 0.002, OR 0), and successful noninvasive ventilation trial were more likely to be ventilated for less than 15 days. Noninvasive ventilation in 92 cases was sufficient in 38%, which was accompanied by a significantly shorter duration of ventilation ($p$ = 0.001) and intensive care unit (ICU) stay ($p$ = 0.01). IV immunoglobulins, plasma exchange, and immunoadsorption were more likely to be combined sequentially if the duration of MV and the stay in an ICU extended ($p$ = 0.0503, OR 2.05). Patients who received plasma exchange or immunoadsorption as first-line therapy needed invasive ventilation significantly less often ($p$ = 0.003). In-hospital mortality was 12%, which was significantly associated with the number of comorbidities (>3) and complications such as acute respiratory distress syndrome and resuscitation. Main cause of death was multiorgan failure, mostly due to sepsis.

### Conclusion

Mortality and duration of MC remained comparable to previous reports despite higher age and a high disease burden in our study. Prevention and treatment of complications and specialized neurointensive care are the cornerstones in order to improve outcome.

MORE ONLINE

**CME Course**
NPub.org/cmelist

*On behalf of the Initiative of German Neurointensive Trial Engagement (IGNITE).

From the Department of Neurology (B.N., K.A., A.V.), University Medical Center Regensburg; NeuroCure Clinical Research Center (P.M., S.K., A.M.) and Departments of Neurology and Experimental Neurology (P.M., A.M.), Charité–Universitätsmedizin Berlin; Berlin Institute of Health (P.M., S.K., A.M.); Department of Neurology (S.S., J.B.), Heidelberg University Hospital; Department of Neurology (J.B.), Klinikum Kassel; Department of Mathematics and Computer Science (U.N.), Philipps-Universität Marburg; Department of Neurology (H.B.H., S.T.G.), University Hospital Erlangen; Department of Neurology (A.T., A.S.), HELIOS Klinikum Erfurt; Department of Neurology (J.D., C.R.), DRK-Kliniken Nordhessen, Kassel; Department of Neurology (H.S., E.S.), University Hospital, Technische Universität Dresden; Department of Neurology (H.S.), Klinikum Augsburg; Department of Neurology (E.S.), Städtisches Klinikum Dresden; Department of Neurology (H.F.), University of Freiburg; Department of Neurology (C.F.), St. Josef-Hospital, Ruhr-University Bochum; Department of Neurology (A.A.), Kliniken Maria Hilf GmbH Mönchengladbach; Hans Berger Department of Neurology (J.Z.), Jena University Hospital; Department of Neurology (C.D., H.R.S.), University of Cologne; and Department of Neurology (C.D.), LVR-Klinik Bonn, Germany.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Coinvestigators are listed in appendix 2 at the end of the article.

## Glossary

**AChR-Ab** = acetylcholine receptor antibody; **CPR** = cardiopulmonary resuscitation; **IA** = immunoadsorption; **ICD-10** = International Classification of Diseases–10; **ICU** = intensive care unit; **IVIg** = IV immunoglobulin; **LOS-h** = length of stay in hospital; **LOS-ICU** = length of stay in intensive care unit; **MANOVA** = multivariate analysis of variance; **MC** = myasthenic crisis; **MG** = myasthenia gravis; **MGFA** = Myasthenia Gravis Foundation of America; **MLE** = maximum likelihood estimate; **MMF** = mycophenolate mofetil; **MTX** = methotrexate; **MuSK-Ab** = muscle-specific tyrosine kinase antibody; **MV** = mechanical ventilation; **NICU** = neurointensive care unit; **NIV** = noninvasive ventilation; **OR** = odds ratio; **PE** = plasma exchange.

Within the first 2 years after the diagnosis of myasthenia gravis (MG), approximately 15%–20% of patients with MG develop a potentially life-threatening myasthenic crisis (MC) with requirement of mechanical ventilation (MV) and extended intensive care management.[1,2]

Until the early 1960s, mortality of MC was >40%. Today, reports on mortality are heterogeneous and usually range between 5% and 12%[1–4] but higher rates up to 22% also have been reported.[5–9] Data on therapy regimens, outcome, and mortality in MC are based mainly on small monocentric cohorts[2,3,6,9–11] or on nationwide registries.[1,4,8,12] The first group is less representative due to the single-center character with a small study population (13–53 patients); the second group exclusively addressed epidemiologic issues and outcome but lacked clinical data. In addition, data might have been biased because of different definitions of crisis including or excluding Myasthenia Gravis Foundation of America (MGFA) Class IV.[2–4] In consequence, reliable data for MC requiring MV (MGFA Class V) from large-enough cohorts hardly exist. There are reports that demographic characteristics in MG—such as an increasing prevalence of elderly—have changed,[13–15] but little is known if this is applicable for MC as well and how it affects therapy and outcome of MC since age and comorbidity are main predictors for survival.[1] Moreover, it is not known whether noninvasive ventilation (NIV), proposed by few monocentric trials,[16–18] is applied in MC to a noteworthy degree in real-world practice.

This study was performed in order to analyze clinical characteristics, treatment, and potential factors affecting outcome and mortality of MC requiring MV in a representative neurocritical care population.

## Methods

### Study design and patient selection

Twelve German Departments of Neurology with specialized neurointensive care units (NICUs) or neurologically associated interdisciplinary intensive care units (ICUs) took part in the study, 4 of which were certified myasthenia centers (thus being specialized in the treatment of MG and fulfilling certain quality standards by the Deutsche Myasthenie Gesellschaft–DMG/German Myasthenia Society). All consecutive patients were retrospectively analyzed if they had MC and required MV. For identification, all patients discharged with the diagnosis of MG according to the ICD-10 (G70.0-70.3) who were treated and ventilated in an ICU between 2006 and 2015 were reviewed. MC was defined as an exacerbation of myasthenic symptoms with bulbar or general weakness requiring MV. Diagnosis of MG had to be established according to national guidelines[19] clinically and confirmed by specific tests (antibody testing or repetitive stimulation or improvement after cholinergic medication). Patients with cholinergic crisis, Lambert-Eaton syndrome, and myasthenic syndromes other than MG (such as congenital MG) were excluded as well as those who required MV due to reasons other than MG (e.g., heart failure or after surgery) and if MV was initiated within 4 weeks after thymectomy to exclude patients with post-thymectomy crisis.

Episodes of MC were counted separately if patients were discharged in their prehospital status and if new triggers for the next crisis could be determined.

### Standard protocol approvals, registrations, and patient consents

Local ethics committees and institutional review boards of the participating centers approved the study based on the central vote of the ethics committee at University of Regensburg (no. 15-101-0259). Patient consent was not necessary after ethic committee approval since solely retrospective data were obtained and patients were anonymized.

### Data acquisition

We obtained data on baseline demographics, clinical features, medication, and comorbidities by reviewing medical charts and institutional databases. MGFA class in the last visit before MC, the most likely factors that precipitated the crisis (multiple answers possible), antibody status, and history of thymoma, and thymectomy were recorded. Data collection regarding treatment regimens included IV immunoglobulin (IVIg), plasma exchange (PE), immunoadsorption (IA), and IV pyridostigmine or neostigmine. MV was categorized as NIV, invasive ventilation, and invasive ventilation after NIV (NIV + invasive ventilation). Data regarding clinical course of MC included duration of ICU stay and days in hospital, duration of MV, predefined complications, in-hospital mortality, and site of referral/discharge. We obtained follow-up data on mortality and outcome from institutional databases after discharge as available.

## Statistics

GraphPad Prism 5 (GraphPad Software, La Jolla, CA) as well as R (The R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. Depending on distribution, data were presented as mean (SD) or median (interquartile range); group comparison was tested with either Student *t* test or Fisher exact test with odds ratios (ORs), respectively. The significance level was set to $\alpha = 0.05$ both-sided. For the calculation of OR, the conditional maximum likelihood estimate (MLE) was used, rather than the unconditional MLE. Duration of ventilation was dichotomized (>15 days vs <15 days). To detect significant differences among group means of metric dependent variables and binary independent variables, a multivariate analysis of variance (MANOVA) was conducted. For the MANOVA, variables with variance zero or more than 30% missing values were not analyzed. Patients who died in hospital, or for whom the date of intubation or the duration of ventilation were not known exactly, were excluded from analysis of "characteristics of patients needing ventilation longer than 15 days" (table 4 and figure 1) in order to exclude bias because of early death.

## Data availability

All analyzed data are published in this article. Raw data (Excel table) will be shared by request from any investigator.

# Results

## Baseline characteristics

Baseline characteristics are displayed in table 1. We identified 250 cases of MC in 223 patients admitted to the 12 participating German centers during a 10-year period. Twenty patients were included with at least 2 independent MCs (maximum number of MCs was 4). The average time between 2 singular crises was 345.5 days. Median age at crisis was 72 years (range 14–89 years); 57% of the patients were male. MC occurred mainly in patients with late-onset MG (202 vs 44 patients) who were also more often men (ratio 1.6:1). If MG was already known before crisis (n = 196), 94% were treated with acetylcholinesterase inhibitors. Azathioprine and prednisolone alone or in combination (prednisolone n = 88, azathioprine n = 36, azathioprine + prednisolone n = 34) were the most commonly used immunosuppressants initiated before or during crisis, followed by mycophenolate mofetil (MMF; n = 4), MMF + prednisolone (n = 4), rituximab + prednisolone (n = 4), methotrexate (MTX) (n = 3), MTX + prednisolone (n = 3), cyclosporine A (n = 3), and rituximab alone (n = 1).

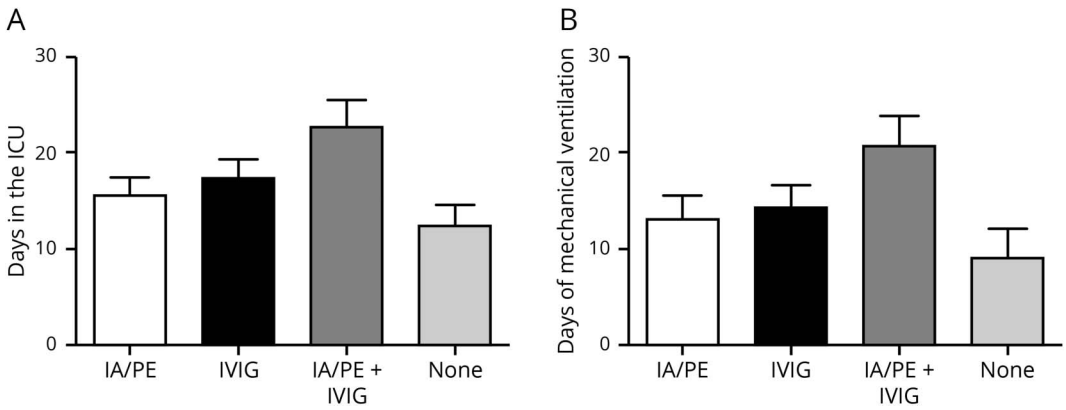
Nearly one-third of the patients (31.2%) had 2 or more chronic diseases besides MG, such as cardiac disease, pulmonary disease, renal insufficiency, diabetes, or neoplasm other than thymoma. A total of 12.8% had more than 2 chronic diseases. Diagnosis of chronic pulmonary disease of any kind (chronic obstructive pulmonary disease, pulmonary fibrosis) was present in 23.1%.

## Clinical features of MG

Clinical features of MG are shown in table 1. The acetylcholine receptor antibody (AChR-Ab) was most frequently detected (212/250 crises, 84.8%). The anti–muscle-specific tyrosine kinase antibody (MuSK-Ab) was present in 19 patients (7.6%) and half of those were also positive for AChR-Ab. There were 17 cases (6.8%) without detectable antibodies (seronegative MG).

Thymoma was present in 74 cases (29.6%). In most cases, thymoma was already treated by surgery and in complete remission at crisis (68%). The status of the tumor had no significant effect on outcome of MC. Thymus hyperplasia was present in 11 patients (4.4%), which is in concordance with the low number of early-onset MG cases in our register. Anti-Titin

**Figure 1** Treatment and outcome




Days in the intensive care unit (ICU) (A) and days of mechanical ventilation (B) of patients who were treated with immunoadsorption (IA) or plasma exchange (PE) (IA/PE; n = 56), IV immunoglobulins (IVIg; n = 66), IA or PE in combination with IVIg treatment (IA/PE + IVIg; n = 43), or without IA, PE, or IVIg (none; n = 34). Decedents (n = 30) and cases where the number of days of ventilation was not known exactly (n = 21, e.g., because of ventilation at discharge or transfers from other hospitals) were excluded. Bars show mean ± SD.

**Table 1** Baseline characteristics of 250 myasthenic crises needing mechanical ventilation

| | No. (%) or mean ± SD (range) |
|---|---|
| **Myasthenic crisis** | 250 |
| **No. of different patients** | 223 |
| **Male/female** | 143/107 (Of crisis) |
| | 130/93 (Of different patients) |
| **Age, y** | 67 ± 15.9 (14–89) |
| **BMI (n = 109)** | 28 ± 9.1 (14.0–67.6) |
| **Pulmonary disease** | 58 (23.2) |
| **Cardiac disease** | 96 (38.4) |
| **Renal insufficiency** | 32 (12.8) |
| **Liver disease** | 11 (4.4) |
| **Diabetes mellitus** | 65 (26.0) |
| **Neoplasm (other than thymoma)** | 38 (15.2) |
| **≥3 Diseases (kidney, cardiac, lung, diabetes, tumor)** | 32 (12.8) |
| **Antibody status** | |
| **AChR** | 212 (84.8) |
| **MuSK** | 19 (7.6; 10 Also with AChR-Ab) |
| **Titin** | 54 (21.6) |
| **Seronegative** | 17 (6.8) |
| **Unknown** | 12 (4.8) |
| **MGFA classification before crisis** | |
| **First manifestation of MG** | 54 (21.6) |
| **Class I** | 13 (5.2) |
| **Class II** | 70 (28) |
| **Class III** | 65 (26) |
| **Class IVa** | 9 (3.6) |
| **Class IVb** | 20 (8.0) |
| **Unknown** | 19 (7.6) |
| **Paraneoplastic MG (thymoma)** | 74 (29.6) (Titin antibodies: 23) |
| **Late-onset** | 202 (80.8) |
| **Early-onset** | 44 (17.6; 4× Unknown) |
| **Thymus hyperplasia** | 11 (4.4) (Titin antibodies: 0) |

Abbreviations: AChR-Ab = acetylcholine receptor antibody; BMI = body mass index; MuSK = muscle-specific receptor tyrosine kinase; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America.
Antibodies unknown due to missing documentation (nevertheless these patients fulfilled the diagnostic criteria for MG).

antibodies were present in 54 cases (all of them positive for AChR-Ab; 3 had additional anti-MuSK-Ab); 23 of these patients had a history of thymoma but none of hyperplasia.

In 94 cases (53.1% of documented scores), MGFA class before MC was IIIa–IVb (table 1). Contrarily, before crisis, MGFA Class I (ocular MG) was reported only in 13 cases (7.3%). Before crisis, in nearly 50% of all cases, patients had been living independently at home; the others were in need of support at home, lived in a care facility, or were hospitalized (table 2). In 54 cases (21.6%), MC occurred as first manifestation of MG.

## Clinical features and course of MC

Clinical features and course of MC are displayed in table 2. The main trigger for crisis was an infection (49.2%); in few cases, more than one reason was reported. The cause of exacerbation of MG remained unknown in 21.5% of all cases. Median duration of MV was 12 days (range 1–219 days); median stay in ICU was 16 days and in hospital 26 days.

MC was treated most often with IVIg (138 cases, 55.2%), either alone (89 cases, 35.6%) or in combination with PE/IA (49 cases, 19.6%; from the known cases, 52.9% received first IVIg and 47.1% first PE or IA). PE was used twice as often as IA (87 vs 43 cases). In 7 cases, IA and PE were combined. Patients who received either IVIg or PE/IA did not differ significantly regarding the duration of MV or days in ICU (figure 1). Comparing the more frequently used PE to IVIg alone, we found no significant differences in duration of MV (14.2 vs 14.2 days) or days in the ICU (16.2 vs 17.2). Both treatment regimens were more likely combined when the duration of MV and the length of stay in ICU extended. In few cases (13.6%), neither IVIg nor PE/IA was applied. In 4 cases, MV was necessary only for 1–3 days, therefore best supportive care seemed to be sufficient. Potassium substitution and best supportive care sufficed in 4 other cases: 16 received continuous pyridostigmine infusion and potassium substitution; in 5 cases, only continuous pyridostigmine infusion was sufficient in order to end crisis and stop ventilation; these patients seemed less severely affected as they required a shorter duration of ventilation (9.1 days vs 13.1 days PE/IA vs 14.2 days IVIg vs 20.8 days combination) and length of stay in ICU was shorter (12.5 days vs 15.7 days PE/IA vs 17.2 days IVIg vs 22.6 days combination) (figure 1). Five patients received best supportive treatment (ventilation, antibiotics) and no immunotherapy such as IVIg or PE/IA. All these 5 patients died within 5 days. There were no differences between subgroups in the choice of treatment regimens with regard to baseline characteristics such as age, antibody status, or MGFA class before crisis.

NIV was performed in 92 crises and sufficed in 35 cases (38.0%) so that intubation was not needed (figure 2). Risk factors for NIV failure (table 3) were crisis due to infection ($p = 0.0006$; OR 5), in most cases pneumonia, and a MGFA Class III–IV before crisis ($p = 0.047$; OR 0.38). The duration of ventilation (mean 6.7 days vs 21.3 days; $p = 0.0002$) and length of stay in ICU (mean 11.1 vs 24.3 days; $p = 0.003$) were shorter in NIV patients than in those with invasive ventilation. Complications, especially the rate of pneumonia,

**Table 2** Data of myasthenic crisis (n = 250)

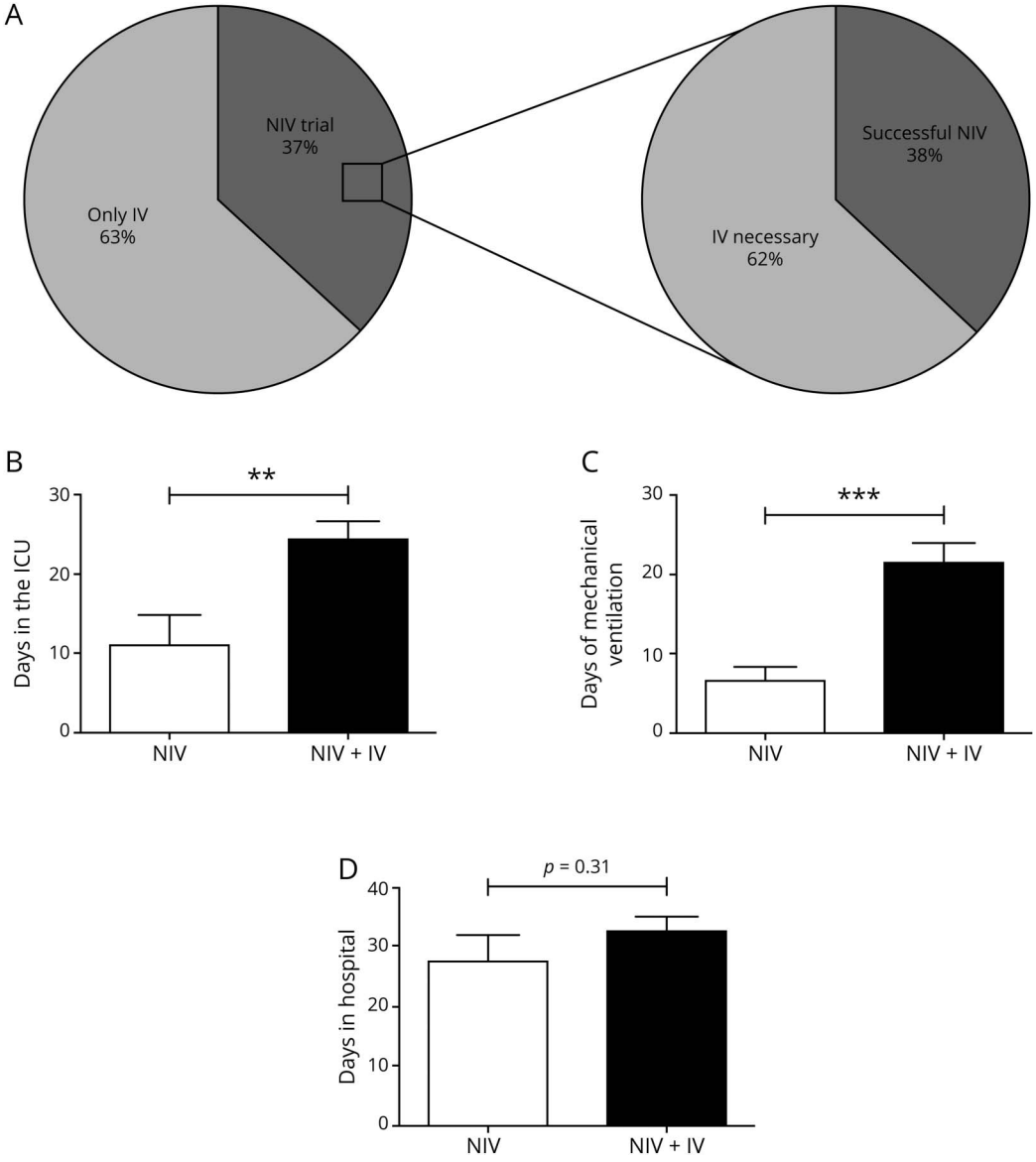
| | No. (%) or mean ± SD (range) |
|---|---|
| **Cause of myasthenic crisis (n = 260)** | |
| **First manifestation of MG** | 54 (20.8) |
| **Infection** | 128 (49.2) |
| **Nonadherence to MG treatments** | 22 (8.5) |
| **Idiopathic/unknown** | 56 (21.5) |
| **Days of mechanical ventilation in the ICU** | 19.4 ± 23.4 (1–219) |
| **Days in the ICU** | 21.7 ± 22.5 (1–202) |
| **Days in the hospital** | 31.1 ± 23.5 (3–203) |
| **Status at discharge (n = 250)** | |
| **Rehabilitation or weaning clinic** | 116 (46.4) |
| **Independent at home** | 30 (12.0) |
| **At home dependent on help** | 15 (6.0) |
| **In a care facility** | 5 (2.0) |
| **Unknown** | 54 (21.6) |
| **Dead** | 30 (12) |
| **Status before crisis (n = 250)** | |
| **Independent at home** | 124 (49.6) |
| **At home dependent on help** | 37 (14.8) |
| **In a care facility or hospital** | 72 (28.8) |
| **Unknown** | 17 (6.8) |
| **Status before crisis was reached at discharge (status at discharge and before crisis known, n = 179)** | 58 (32.4) |
| **Ventilation after discharge necessary (in rehabilitation or weaning clinic)** | 45 (20.5 of survivors) |
| **Status at first follow-up (mean after 17.5 weeks, range 1–80 weeks; n = 77)** | |
| **Independent at home** | 40 (51.9) |
| **At home dependent on help** | 22 (28.6) |
| **In a care facility** | 14 (18.2) |
| **Dead** | 1 (1.3) |
| **Cause of death in hospital (n = 30)** | |
| **Sepsis with MODS or MODS without known reason** | 14 (46.7) |
| **CPR because of heart failure and poor outcome** | 6 (20) |
| **Termination of ICU treatment because of age and multiple other diseases** | 3 (10) |
| **Respiratory insufficiency or ARDS** | 4 (13.3) |
| **Severe pulmonary embolism** | 1 (3.3) |
| **Spontaneous subarachnoid bleeding** | 1 (3.3) |
| **Intracerebral bleeding** | 1 (3.3) |
| **Complications (n = 250)** | |
| **Atelectasis** | 42 (16.8) |
| **Pneumonia/infectious bronchitis** | 136 (54.4) |
| **ARDS** | 11 (4.4) |
| **Urinary tract infection** | 35 (14.0) |
| **Diarrhea caused by *Clostridium difficile*** | 5 (2.0) |
| **Diarrhea of other cause** | 22 (8.8) |
| **Delirium/psychosis** | 38 (15.2) |
| **Pneumothorax** | 10 (4.0) |
| **Sepsis** | 49 (19.6) |
| **Gastrointestinal bleeding** | 9 (3.6) |
| **Asystolia or tachycardia needing CPR** | 25 (10.0) |
| **Treatment of the crisis (n = 250)** | |
| **Treatment with IVIg** | 138 (55.2) |
| **Treatment with PE or IA** | 123 (49.2) (87 × PE/43 × IA/7 × both, 49 were also treated with IVIg + PE or IA) |
| **No IVIg, PE, or IA treatment** | 34 (13.6) |
| **Unknown** | 2 (0.8) |
| **Continuous pyridostigmine infusion** | 105 (42.0) |
| **Continuous potassium infusion** | 118 (47.2) |

Abbreviations: ARDS = acute respiratory distress syndrome; CPR = cardiopulmonary resuscitation; IA = immunoadsorption; ICU = intensive care unit; IVIg = IV immunoglobulin; MG = myasthenia gravis; MODS = multiple organ dysfunction syndrome; PE = plasma exchange.

were significantly lower in NIV patients (table 3). The antibody status had no influence on success of NIV trial. Interestingly, patients with PE or IA as first-line therapy needed invasive ventilation significantly less often ($p$ = 0.003; OR 4.49). If not successful, the NIV trial did not extend the duration of ventilation compared to patients who were intubated primarily without NIV trial (mean 21.3 days in NIV + invasive ventilation vs 21.7 days in invasive ventilation); baseline characteristics did not differ between the groups (data not shown).

Patients ventilated for more than 15 days were significantly older ($p$ = 0.001), more often had late-onset MG ($p$ = 0.0001; OR 4.5), had a higher MGFA class before crisis ($p$ = 0.0001 for IVb; OR infinite), and more frequently had at least 3 chronic diseases (especially cardiac disease and diabetes mellitus) ($p$ = 0.02; OR 2.99; table 4)

**Figure 2** Noninvasive ventilation (NIV) treatment




(A) Percentage of cases where NIV was attempted before intubation (n = 92 out of 250 cases) and the rate of successful NIV trials as well as the percentage of cases where intubation was necessary. Days in the intensive care unit (ICU) (B), days of mechanical ventilation (C), and days in the hospital (D) of patients treated with NIV only (n = 35) compared to cases where NIV trial was not successful (n = 57). IV = invasive ventilation. Bars show mean ± SD. $^{**}p < 0.01$, $^{***}p < 0.001$ (*t* test).

compared with those with shorter ventilation. Furthermore, pneumonia ($p = 0.0001$; OR 3.13) and cardiopulmonary resuscitation (CPR) ($p = 0.0008$; OR 9.15) were associated with ventilation for >15 days. The treatment regimens did not differ significantly, although a combination of PE or IA with IVIg was common in patients with ventilation >15 days, but this was not significant ($p = 0.0503$; OR 2.05; table 4). On the other hand, especially patients with early-onset MG ($p = 0.0001$, OR 0.21), thymus hyperplasia ($p = 0.002$, OR 0), and successful NIV trial (figure 2) were more likely to be ventilated for less than 15 days. The antibody status had no influence on duration of ventilation.

## Complications

Complications are displayed in table 2 and consisted primarily of pneumonia (54.4%), sepsis (19.6%), atelectasis (16.8%), delirium (15.2%), and urinary tract infection (14%). CPR—mostly due to cardiogenic shock (e.g., cardiac arrest, arrhythmia)—was performed in 25 cases (10%). There was no association between CPR because of asystolia/tachycardia and continuous IV application of acetylcholinesterase inhibitors. All analyzed complications had an influence on the length of stay in hospital (LOS-h), length of stay in ICU (LOS-ICU), or days of MV in a different manner. Gastrointestinal bleedings were rare (n = 9) but had a highly significant influence on LOS-h ($p < 0.0001$), LOS-ICU ($p < 0.0001$), and MV ($p = 0.0004$) in

**Table 3** Noninvasive ventilation (NIV) vs invasive ventilation

| Patients | NIV (n = 35) | NIV + invasive ventilation (n = 57) | *p* Value | OR |
|---|---|---|---|---|
| **Basic data** | | | | |
| **Age, y** | 66.5 ± 14.7 (24–88) | 66.6 ± 16.5 (23–87) | 0.99 | |
| **Male/female** | 16/19 | 34/23 | 0.20 | 0.57 |
| **Pulmonary disease** | 9 (25.7) | 13 (22.8) | 0.80 | 1.16 |
| **Cardiac disease** | 10 (28.6) | 19 (33.3) | 0.82 | 0.81 |
| **Liver disease** | 0 (0.0) | 2 (3.5) | 0.53 | 0 |
| **Diabetes mellitus** | 10 (28.6) | 18 (31.6) | 0.82 | 0.87 |
| **Neoplasm (other than thymoma)** | 8 (22.9)[a] | 3 (5.3)[a] | 0.02[a] | 5.23[a] |
| **Dialysis** | 0 (0.0) | 1 (1.8) | 1.0 | 0 |
| **Smoker** | 4 (11.4) | 4 (7.0) | 0.47 | 1.70 |
| **Alcohol addicted** | 0 (0.0) | 3 (5.3) | 0.29 | 0 |
| **≥3 Diseases (kidney, cardiac, lung, diabetes, tumor)** | 4 (11.4) | 6 (10.5) | 1.0 | 1.10 |
| **Myasthenia gravis** | | | | |
| **Early-onset** | 6 (17.1) | 8 (14.0) | 0.77 | 1.26 |
| **Late-onset** | 29 (82.9) | 49 (86.0) | 0.77 | 0.79 |
| **Paraneoplastic MG** | 12 (34.3) | 24 (42.1) | 0.51 | 0.72 |
| **Thymus hyperplasia** | 2 (5.7) | 2 (3.5) | 0.63 | 1.66 |
| **MGFA classification before crisis** | | | | |
| **First manifestation of MG** | 7 (20.0)[a] | 9 (15.8)[a] | 0.047 For Class III and IV[a] | 0.38[a] |
| **Class I** | 0 (0.0)[a] | 3 (5.3)[a] | | |
| **Class II** | 15 (42.8)[a] | 17 (29.8)[a] | | |
| **Class III** | 8 (22.9)[a] | 18 (31.5)[a] | | |
| **Class IVa** | 0 (0.0)[a] | 1 (1.8)[a] | | |
| **Class IVb** | 0 (0.0)[a] | 6 (10.5)[a] | | |
| **Unknown** | 5 (14.3)[a] | 3 (5.3)[a] | | |
| **Status before crisis** | | | | |
| **Independent at home** | 17 (48.6) | 24 (42.1) | 0.67 | 1.29 |
| **At home dependent on help** | 4 (11.4)[a] | 17 (29.8)[a] | 0.045[a] | 0.31[a] |
| **In a care facility or hospital** | 12 (34.3) | 13 (22.8) | 0.24 | 1.75 |
| **Unknown** | 2 (5.7) | 3 (5.3) | 1 | 1.09 |
| **Cause of crisis** | | | | |
| **Infection** | 15 (42.9)[a] | 45 (73.8)[a] | 0.0006[a] | 0.20[a] |
| **First manifestation of MG** | 7 (20.0) | 9 (14.8) | 0.77 | 1.32 |
| **Nonadherence to MG treatments** | 1 (2.9) | 1 (1.6) | 1 | 1.64 |
| **Idiopathic/unknown** | 12 (34.3) | 6 (9.8) | 0.64 | 1.33 |
| **Therapy** | | | | |
| **IVIg** | 20 (57.1)[a] | 45 (78.9)[a] | 0.034[a] | 0.36[a] |
| **PE or IA** | 19 (54.3)[a] | 16 (28.1)[a] | 0.016[a] | 3.04[a] |

Continued

**Table 3** Noninvasive ventilation (NIV) vs invasive ventilation *(continued)*

| Patients | NIV (n = 35) | NIV + invasive ventilation (n = 57) | *p* Value | OR |
|---|---|---|---|---|
| **PE or IA + IVIg** | 7 (20.0) | 11 (19.3) | 1.0 | 1.05 |
| **PE or IA as first-line therapy** | 16 (45.7)[a] | 9 (15.8)[a] | 0.003[a] | 4.49[a] |
| **Complications** | | | | |
| **Pneumonia** | 6 (17.1)[a] | 36 (63.2)[a] | <0.0001[a] | 0.12[a] |
| **ARDS** | 0 (0.0) | 4 (7.0) | 0.29 | 0 |
| **CPR** | 0 (0.0) | 4 (7.0) | 0.29 | 0 |
| **Sepsis** | 5 (14.3) | 14 (24.6) | 0.30 | 0.52 |

Abbreviations: ARDS = acute respiratory distress syndrome; CPR = cardiopulmonary resuscitation; IA = immunoadsorption; IVIg = IV immunoglobulin; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; OR = odds ratio; PE = plasma exchange.
*t* Test was used for statistical analysis of age differences and for comparison of days of mechanical ventilation in the intensive care unit, days in the intensive care unit, and days in the hospital. For other measures, the Fisher exact test with ORs was used. Thirty patients who required only NIV were compared with 57 patients who received NIV first, but in whom invasive ventilation was necessary later (NIV + invasive ventilation). Values are mean ± SD (range) or n (%).
[a] Statistically significant results.

MANOVA testing. Conditions needing CPR (LOS-h $p = 0.002$, LOS-ICU $p < 0.0001$, MV $p = 0.01$), delirium (LOS-h $p = 0.088$, LOS-ICU $p = 0.002$, MV $p = 0.001$), and sepsis (LOS-h $p = 0.003$, LOS-ICU $p = 0.002$, MV $p = 0.12$) were the complications with the strongest influence and occurred more frequently. Urinary tract infection (LOS-h $p = 0.06$, LOS-ICU $p = 0.19$, MV $p = 0.004$), pneumonia (LOS-h $p = 0.8$, LOS-ICU $p = 0.048$, MV $p = 0.12$), and atelectasis (LOS-h $p = 0.006$, LOS-ICU $p = 0.31$, MV $p = 0.26$) had less effect.

## Outcome/mortality

At discharge from the hospital, MV was still necessary in 20.5% of all survivors. These patients were significantly older ($p = 0.01$), more often had late-onset MG ($p = 0.01$; OR 4.26), severity of MG before crisis was higher (MFGA Class III and IV $p = 0.006$; OR 2.58), and patients more often had ≥3 chronic diseases ($p = 0.0001$; OR 5.99) in comparison with those without ongoing MV. In particular, a chronic cardiac disease ($p = 0.003$; OR 2.79) and diabetes ($p = 0.002$; OR 2.97) made it more likely that patients still required MV at discharge. The majority of patients were transferred to a rehabilitation facility (46.4%; table 2). In-hospital mortality was 12.0% (30/250 cases), which was significantly associated with ≥3 comorbidities and complications such as acute respiratory distress syndrome and CPR (table 5); deceased patients were on average older (70.9 ± 11.6 [44–87] years vs 65.5 ± 16.7 [14–89] years), but this was statistically not significant ($p = 0.09$). Status before crisis (table 2) had no influence on survival. Main cause of death (n = 14) was multiorgan failure, mostly due to sepsis. Four patients died due to respiratory insufficiency despite ICU treatment and in 3 cases therapy was switched to palliative care according to the patient's alleged will because of age, severe medical comorbidity, and complications. Mean age at death was 70.9 years (SD 11.6 years).

## Follow-up

Follow-up data were available for 77 cases only (table 2; 35% of survivors, mean 17.5 weeks, median 10 weeks, range 1–80 weeks after discharge). At follow-up, in about 50% of all known cases, patients lived back home again either completely independent or needing some support (e.g., ambulatory care service). One death was reported.

In the subgroup analysis of patients with MC as the first manifestation of MG (data not shown), baseline characteristics were not different than in others (established MG) except that patients were older (mean 68.7 vs 65.1 years, not significant). Nonetheless, duration of ventilation (mean 18.3 vs 19.8 days, not significant) and days in the ICU (mean 18.8 vs 22.6 days, not significant) were shorter while rate of NIV was slightly higher (15.2% vs 13.9%), with a clearly higher success rate of NIV trial (58.3% vs 34.2%; $p = 0.1$). When transferred to rehabilitation, patients in this subgroup were less frequently in need for MV (10.9% vs 20.8%, not significant) and in-hospital mortality (6.5% vs 12.5%, not significant) was lower but that was not significant for both. There were no differences between the groups in frequency or types of complications during crisis.

# Discussion

We analyzed 250 MCs in 223 individual patients, representing the largest multicenter study on MCs to date. Patients were cared for at specialized NICUs or ICUs in 10 tertiary referral centers (9 of these university hospitals) and 2 large regional hospitals, hence reflecting nationwide coverage with considerable diversity in infrastructure, geographical features, and standard of care diversity, constituting a large study population representative of most patients with severe MC in Germany.

The in-hospital mortality of 12% in our cohort is higher than that reported in some previous studies[1–4,11] with a mortality of 5%–10%. Thomas et al.[2] reported a mortality of 4% (3/73) in the ICU increasing to 9.6% (7/73) considering the whole in-hospital mortality. In a study of 38 patients with MG[3] with

**Table 4** Characteristics of patients needing ventilation longer than 15 days

| | Ventilation >15 days (n = 89) | Ventilation ≤15 days (n = 110) | *p* Value | OR |
|---|---|---|---|---|
| **Basic data** | | | | |
| **Age, y** | 69.4 ± 13.9 (25–89)[a] | 61.6 ± 18.4 (14–84)[a] | 0.001[a] | |
| **Male/female** | 56/33 | 56/54 | 0.11 | 1.63 |
| **Pulmonary disease** | 23 (25.8) | 24 (21.8) | 0.51 | 1.25 |
| **Cardiac disease** | 37 (41.6)[a] | 30 (27.3)[a] | 0.04[a] | 1.89[a] |
| **Liver disease** | 4 (4.5) | 2 (1.8) | 0.41 | 2.53 |
| **Diabetes mellitus** | 32 (36.0)[a] | 21 (19.1)[a] | 0.01[a] | 2.37[a] |
| **Neoplasm (other than thymoma)** | 9 (10.1) | 17 (15.5) | 0.30 | 0.62 |
| **Dialysis** | 1 (1.1) | 1 (0.9) | 1.0 | 1.24 |
| **Smoker** | 10 (11.2) | 5 (4.5) | 0.10 | 2.65 |
| **Alcohol addicted** | 4 (4.5) | 1 (0.9) | 0.17 | 5.09 |
| **≥3 Diseases (kidney, cardiac, lung, diabetes, tumor)** | 17 (19.1)[a] | 8 (7.3)[a] | 0.02[a] | 2.99[a] |
| **MG** | | | | |
| **Early-onset** | 7 (8.0; 1 Unknown)[a] | 32 (29.6; 2 Unknown)[a] | 0.0001[a] | 0.21[a] |
| **Late-onset** | 81 (92.0)[a] | 76 (70.4)[a] | 0.0001[a] | 4.50[a] |
| **Paraneoplastic MG** | 28 (31.5) | 33 (30.0) | 0.88 | 1.07 |
| **Thymus hyperplasia** | 0 (0.0)[a] | 10 (9.1)[a] | 0.002[a] | 0[a] |
| **MGFA classification before crisis** | | | | |
| **First manifestation of MG** | 20 (22.5)[a] | 27 (24.5)[a] | 0.03 For FM Class II[a] | 0.52[a] |
| **Class I** | 6 (6.7) | 6 (5.5) | | |
| **Class II** | 18 (20.2)[a] | 39 (35.5)[a] | | |
| **Class IIIa** | 26 (29.2)[a] | 27 (24.6)[a] | <0.0001 For Class IVb[a] | |
| **Class IVa** | 3 (3.4)[a] | 5 (4.5)[a] | | Inf[a] |
| **Class IVb** | 12 (13.5)[a] | 0 (0.0)[a] | | |
| **Unknown** | 4 (4.5)[a] | 6 (5.5)[a] | | |
| **Status before crisis** | | | | |
| **Independent at home** | 38 (42.7)[a] | 68 (61.8)[a] | 0.01 For independent at home and for at home dependent[a] | 0.46[a] |
| **At home dependent on help** | 21 (23.6)[a] | 11 (10.0)[a] | | 2.76[a] |
| **In a care facility or hospital** | 26 (29.2)[a] | 23 (20.9)[a] | | 1.56[a] |
| **Unknown** | 4 (4.5)[a] | 8 (7.3)[a] | | 0.6[a] |
| **Cause of crisis** | | | | |
| **Infection** | 49 (53.3) | 55 (47.4) | NS for all tested variants | 1.22 |
| **First manifestation of MG** | 20 (21.7) | 27 (23.3) | | 0.89 |
| **Nonadherence to MG treatments** | 9 (10.0) | 7 (6.0) | | 1.65 |
| **Idiopathic/unknown** | 14 (15.2) | 27 (23.3) | | 0.58 |
| **Therapy** | | | | |
| **IVIg** | 57 (64.0) | 56 (50.9) | 0.084 | 1.72 |

Continued

**Table 4** Characteristics of patients needing ventilation longer than 15 days *(continued)*

| | Ventilation >15 days (n = 89) | Ventilation ≤15 days (n = 110) | *p* Value | OR |
|---|---|---|---|---|
| **PE or IA** | 48 (53.9) | 52 (47.3.1) | 0.39 | 1.31 |
| **PE or IA + IVIg** | 23 (25.8) | 16 (14.5) | 0.05 | 2.05 |
| **PE or IA as first-line therapy** | 34 (38.2) | 40 (36.4) | 0.88 | 1.08 |
| **Pneumonia** | 61 (68.5)[a] | 45 (40.9)[a] | 0.0001[a] | 3.13[a] |
| **CPR** | 13 (14.6)[a] | 2 (1.8)[a] | 0.0008[a] | 9.15[a] |
| **Sepsis** | 21 (23.6) | 15 (13.6) | 0.09 | 1.95 |

Abbreviations: CPR = cardiopulmonary resuscitation; FM = first manifestation of myasthenia gravis; IA = immunoadsorption; IVIg = IV immunoglobulin; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; NS = not significant; OR = odds ratio; PE = plasma exchange.
*t* Test was used for statistical analysis of age differences, Fisher exact test with ORs for other measures. A total of 89 patients who needed mechanical ventilation for more than 15 days were compared with 110 patients who needed mechanical ventilation for a maximum of 15 days. Deceased patients (n = 30) and cases where the number of days of ventilation was not known exactly (n = 21, e.g., because of ventilation at discharge or transfers from other hospitals) were excluded. Values are mean ± SD (range) or n (%).
[a] Statistically significant results.

exacerbation of symptoms, mortality was 8%, even though 10/38 patients did not require MV (NIV or intubation) and therefore did not have a severe MC, as did patients in our cohort. Other studies[5–7] reported a higher mortality than ours with 14%–17%. Furthermore, in a study by Damian et al.,[8] ICU mortality was 8.5%, but increased to 22% if based on the whole hospital stay; the authors discussed that the main reasons were unreliable predictors for extubation success in MC and (premature) discharge of patients to general medical wards with insufficient experience with myasthenic conditions. Some patients in this study were not treated in a NICU, which argues for treatment of MC at NICUs or specialized ICUs with full neurologic support. Hence, our mortality rate of 12% lies somewhat in the middle of the range reported so far. Given the population size of our study, this finding may be the most valid to date.

There might have been a selection bias towards more severe cases because all participating centers have specialized referral NICUs or ICUs or have specialized certified MG centers (treating 61.6% of cases); a high proportion of our patients had an MGFA severity Class ≥III last reported before crisis (38%) or paraneoplastic MG (29.6%, compared to 10%–15% in common MG populations). In concordance with earlier studies,[2,6,20] thymoma is a well-known risk factor for severe symptoms of MG and crisis. Moreover, with a median age of 72 years, our patients were notably older than in all earlier studies.[1–11,16,18,21–24] Consistently, 81% of the patients in our study had late-onset MG and a high rate of comorbidities. Although decedents were older than survivors, there was no significant correlation of age and mortality in our study; the burden of chronic disease, however, was a risk factor for mortality. Age and comorbidities have been described as risk factors for longer intubation and poor outcome before.[1,2,6]

With the latter aspect, for the first time, our study supports the notion that the frequency of MC is increasing in older patients, which might be attributed to the increasing incidence of MG in the older population as described elsewhere[13–15] and probably more patients with MG reaching an older age. In addition, we observed a high rate of MC as the first manifestation of MG (54 cases, 21.6%); other smaller cohorts found rates over 40%,[3,4] which should be considered in clinical practice for respiratory insufficiency of undetermined origin, especially in the elderly. As another epidemiologic note, older studies from the 1990s[2,9] report a majority of female patients with MC while more recent ones[4]—including our own—describe more male patients. The predominance of male sex in our cohort may be based on the fact that late-onset MG occurs more frequently in male patients.[20,25]

Similar to earlier reports,[3,20,26,27] median duration of MC and MV, respectively, was 12 days, LOS-ICU 16 days, and LOS-h 26 days. With respect to the aforementioned circumstances, it is remarkable that clinical course and mortality remained stable over the last decades.

Treatment for MC with IVIg increased during the last decades, as described in several reports,[1,4,5,9] probably due to its easier management compared to PE/IA and since it has been shown to be as efficient as PE.[28–30] According to some reports,[31] treatment with IVIg should be preferred to PE in older patients and those with several comorbidities because of an alleged higher incidence of (cardiopulmonary and infectious) complications under PE in this population. In our cohort, patients were most commonly treated with IVIg. Nonetheless, decision for a sequential combination of both treatment regimens was frequent, which was probably due to a prolonged and severe course of crisis associated with a prolonged stay in an ICU and prolonged duration of ventilation, respectively. IA was used in 42 cases and combined with PE in 6 cases since there have been reports that IA or a combination of IA and PE might be superior to PE alone,[23,24] especially for prolonged cases of MC. Interestingly, in patients with NIV, intubation was less likely required if PE or IA was applied as first-line therapy, whereas the

**Table 5** Characteristics of survivors and deceased in myasthenic crisis

| | Deceased (n = 30) | Survivors (n = 220) | *p* Value | OR |
|---|---|---|---|---|
| **Basic data** | | | | |
| **Age, y** | 70.9 ± 11.6 (44–87) | 65.5 ± 16.7 (14–89) | 0.09 | |
| **Male/female** | 19/11 | 124/96 | 0.56 | 1.34 |
| **Pulmonary disease** | 5 (16.7) | 53 (24.1) | 0.49 | 0.63 |
| **Cardiac disease** | 17 (56.7)[a] | 79 (35.9)[a] | 0.04[a] | 2.33 |
| **Liver disease** | 3 (10) | 8 (3.6) | 0.13 | 2.93 |
| **Diabetes mellitus** | 8 (26.7) | 57 (25.9) | 1.00 | 1.04 |
| **Neoplasm (other than thymoma)** | 8 (26.7) | 30 (13.6) | 0.10 | 2.29 |
| **Dialysis** | 0 (0.0) | 3 (1.4) | 1.0 | 0 |
| **Smoker** | 5 (16.7) | 16 (7.3) | 0.15 | 2.54 |
| **Alcohol addicted** | 1 (3.3) | 7 (3.2) | 0.47 | 1.86 |
| **≥3 Diseases (kidney, cardiac, lung, diabetes, tumor)** | 8 (26.7)[a] | 24 (10.9)[a] | 0.035[a] | 2.95 |
| **MG** | | | | |
| **Early-onset** | 4 (13.8; 1 Unknown) | 40 (18.4; 3 Unknown) | 0.81 | 0.82 |
| **Late-onset** | 25 (86.2) | 177 (81.6) | 0.81 | 1.21 |
| **Paraneoplastic MG** | 7 (23.3) | 67 (30.5) | 0.53 | 0.70 |
| **Thymus hyperplasia** | 0 (0.0) | 11 (5.0) | 0.37 | 0 |
| **MGFA classification before crisis** | | | | |
| **First manifestation of MG** | 3 (10.0) | 51 (23.2) | 0.08 For FM + Class I[a] | 0.38 for FM + Class I[a] |
| **Class I** | 1 (3.3) | 12 (5.5) | | |
| **Class II** | 9 (30.0) | 61 (27.7) | | |
| **Class III** | 8 (26.6) | 57 (25.9) | | |
| **Class IVa** | 1 (3.3) | 8 (3.6) | | |
| **Class IVb** | 3 (10.0) | 17 (7.7) | | |
| **Unknown** | 5 (16.7) | 14 (6.4) | | |
| **Cause of crisis** | | | | |
| **Infection** | 12 (40.0) | 116 (50.4) | NS for all tested variants | 0.60 |
| **First manifestation of MG** | 3 (10.0) | 51 (22.2) | | 0.37 |
| **Nonadherence to MG treatments** | 4 (13.3) | 18 (7.8) | | 1.72 |
| **Idiopathic/unknown** | 11 (36.7) | 45 (19.6) | | 2.24 |
| **Pneumonia** | 20 (66.7) | 116 (52.7) | 0.17 | 1.79 |
| **ARDS** | 7 (23.3)[a] | 4 (1.8)[a] | <0.0001[a] | 16.07 |
| **CPR** | 9 (30.0)[a] | 16 (7.3)[a] | 0.0008[a] | 5.41 |
| **Sepsis** | 12 (40)[a] | 37 (16.8)[a] | 0.006[a] | 3.28 |

Abbreviations: ARDS = acute respiratory distress syndrome; CPR = cardiopulmonary resuscitation; FM = first manifestation of myasthenia gravis; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; NS = not significant; OR = odds ratio.
*t* Test was used for statistical analysis of age differences, Fisher exact test with ORs for other measures. Thirty patients who died during their crisis were compared with the 220 survivors. Values are mean ± SD (range) or n (%).
[a] Statistically significant results.

administration of IVIg seemed not to be sufficient. This could be explained by the faster effect of PE or IA compared to the mechanism of IVIg.

In 34 cases, no therapy with IVIg or IA/PE was performed. In 25 of these cases, patients received IV substitution of pyridostigmine or potassium, which are mentioned as a treatment option in the German guidelines.[19] Only 9 patients received no specific treatment. The circumstances that prompted the attending physician not to follow national or international guidelines in these cases remain unclear due to retrospective data. In total, patients not treated with IVIg or IA/PE needed MV for a shorter time—the difference was not significant—leading to the conclusion that these crises might have been less severe. Biomarkers to predict which therapy will improve MC or why some patients remain refractory to first-line therapy are lacking. In this context, it is important to note that a fifth of our patients still required ventilation after the treatment and when transferred to a rehabilitation facility. This resembles earlier reports where 20%–25% of all patients remained intubated after 1 month of crisis.[2,4] Whether this is due to the MG itself or other causes, such as ICU-acquired weakness, has not yet been investigated. In order to reduce cases with prolonged crisis and complication rates, new biomarkers, therapeutic options for MC, and improvements in intensive care and especially ventilator management are needed.

The high rate of cases with dual antibody positivity (10/19 MuSK-Ab+ were also AChR-Ab+) is remarkable. To our knowledge, there are only 2 studies on MC or exacerbation of MG[3,4] that adequately demonstrate an antibody profile since MuSK-Ab became known. MuSK-Ab was positive in 7.6% in our study and lies in the middle of the range reported so far. None of the 2 studies reported a dual antibody positivity. Otherwise, there are primarily studies on the MuSK-Ab profile in MG only and not in MC. A transfer of results is therefore only possible with caution. Dual antibody positivity has been reported in about 14% of MG cases in just a single study.[32] Thus the question arises whether dual antibody positivity is particularly often associated with a crisis in comparison to other antibody profiles. Perhaps our results also indicate that MuSK-Ab has been underdiagnosed in MC so far. However, in our study the antibody profile had no effect on the course of crisis or outcome as outlined before. Further studies on this topic are needed.

NIV showed positive effects on the frequency of intubation and duration of ventilator assistance in patients with MC in several monocentric and retrospective studies[16–18,33] with more than half of all NIV trials (about 20% of all MC) being successful. In our study, representing real-world practice in a multicenter setting, more than one-third of all NIV trials sufficed so that intubation was not necessary. At the same time, duration of ventilator assistance and rate of complications were reduced, which is in concordance with earlier reports. In case of (imminent) respiratory failure due to MG, it is conceivable that NIV might be able to bridge crisis or prevent the full extent of it by giving the patient the necessary breather with ventilatory assistance. Review of the literature and our data support the notion that NIV might provide sufficient respite to eligible patients until fast-acting procedures such as PE or IA exert their effect. Intubation, on the other hand, usually requires more medication (e.g., sedatives) than NIV and may increase the risk of ventilator-associated pneumonia, which may explain prolonged MV and stay in an ICU, respectively. Preselection of appropriate patients for an NIV trial is crucial for success.[33] Our data suggest that patients in whom pneumonia as the trigger of MC is ruled out, patients with first manifestation of MG at crisis, and patients with a lower MGFA class (< Class III) before crisis seem to be eligible for an NIV trial. However, a bias by preselection by physicians in our cohort must be discussed. In contrast, patients with a higher MGFA class before crisis, severe dysphagia, absent protective reflexes, and who do not tolerate an NIV mask should be intubated early. A higher proportion of more severely affected patients and a supposed high diversity of NIV protocols between the study centers may have led to a lower success rate of NIV in our study than reported.[16–18,33] Nevertheless, NIV might be considered in appropriate patients before intubation as we did not observe prolongation of ventilation when it failed; we saw a shorter duration of ventilation and hospital stay when it was successful. To identify eligible patients for an NIV trial and factors for NIV failure, we are in need of prospective studies.

Limitations of this study arise from its retrospective nature and the fact that MG and MC are rare diseases. The latter was overcome to some extent by a multicenter cohort. On the other hand, there might have been a selection bias towards more severe cases because all participating centers are specialized referral NICUs or ICUs or have specialized certified MG centers and thereby results might not be generalized to all patients with MC. Since our study is retrospective, treatments or diagnostic procedures that were unnecessary or underestimated cannot be excluded. Long-term follow-up results might not be representative due to the retrospective nature and small number of available data.

We demonstrate that clinical characteristics of patients with MC have changed compared to previous reports: MC often occurs as first manifestation of MG, patients are older than reported before and are more often male, onset of MG is predominantly late, and MGFA class before crisis and burden of comorbidities are high. Clinical course depends on comorbidities, age, onset of MG, MGFA class before crisis, and complications during crisis (e.g., sepsis). Nevertheless, duration of crisis, LOS-ICU, and LOS-h as well as in-hospital mortality remained stable during the last 3 decades. IVIg and PE/IA are applied to a similar degree in Germany; a prolonged course of MC, however, often leads to a combination of both regimens. The application of NIV appears to be safe in MC and might suffice under certain circumstances—

especially in combination with early PE or IA—so that intubation becomes unnecessary and length of crisis and ICU stay decrease. A better understanding of specialized neurointensive care in MG, treatment regimens adjusted to the course of the crisis, and specialized ventilator management (e.g., NIV trial in eligible patients) are essential in order to improve outcome.


## Acknowledgment

P.M. is a fellow of the Charité-BIH Clinician Scientist Program.

## Study funding

No targeted funding reported.


## Disclosure

B. Neumann and K. Angstwurm report no disclosures relevant to the manuscript. P. Mergenthaler is on the Advisory Board of HealthNextGen Inc. and has equity interest in the company. S. Kohler and S. Schönenberger report no disclosures relevant to the manuscript. J. Bösel reports personal fees from Medtronic, personal fees from Zoll, personal fees from Boehringer Ingelheim, personal fees from Sedana Medical, and grants from PCORI outside the submitted work. U. Neurmann, A. Vidal, H. Huttner, S. Gerner, A. Thieme, A. Steinbrecher, J. Dunkel, C. Roth, H. Schneider, E. Schimmel, H. Fuhrer, C. Fahrendorf, A. Alberty, and J. Zinke report no disclosures relevant to the manuscript. A. Meisel reports personal fees from Alexion, personal fees from Grifols, grants from Octapharma, and personal fees from Hormosan outside the submitted work. C. Dohmen and H. Stetefeld report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.


## Publication history

Received by *Neurology* February 27, 2019. Accepted in final form July 11, 2019.


**Appendix 1** Authors

| Name | Location | Role | Contribution |
|---|---|---|---|
| **Bernhard Neumann, MD** | University Medical Center Regensburg, Regensburg, Germany | Author | Conception and design of the study, acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Klemens Angstwurm, MD** | University Medical Center Regensburg, Regensburg, Germany | Author | Conception and design of the study, acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Philipp Mergenthaler, MD** | Charité–Universitätsmedizin Berlin, Berlin | Author | Acquisition and analysis of data |
| **Siegfried Kohler, MD** | Charité–Universitätsmedizin Berlin, Berlin | Author | Acquisition and analysis of data |
| **Silvia Schönenberger, MD** | Heidelberg University Hospital, Heidelberg, Germany | Author | Acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Julian Bösel, MD** | Heidelberg University Hospital, Heidelberg, Germany | Author | Acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Ursula Neumann, PhD** | Philipps-Universität Marburg, Marburg, Germany | Author | Acquisition and analysis of data |
| **Amelie Vidal** | University Medical Center Regensburg, Regensburg, Germany | Author | Acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Stefan T. Gerner, MD** | University Hospital Erlangen, Erlangen, Germany | Author | Acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Hagen B. Huttner, MD** | University Hospital Erlangen, Erlangen, Germany | Author | Acquisition and analysis of data |
| **Andrea Thieme, MD** | HELIOS Klinikum Erfurt, Erfurt, Germany | Author | Acquisition and analysis of data |
| **Andreas Steinbrecher, MD** | HELIOS Klinikum Erfurt, Erfurt, Germany | Author | Acquisition and analysis of data |
| **Juliane Dunkel, MD** | DRK-Kliniken Nordhessen, Kassel, Kassel, Germany | Author | Acquisition and analysis of data |
| **Christian Roth, MD** | DRK-Kliniken Nordhessen, Kassel, Kassel, Germany | Author | Acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Haucke Schneider, MD** | University Hospital, Technische Universität Dresden, Dresden, Germany | Author | Acquisition and analysis of data |

Continued

## Appendix 1 *(continued)*

| Name | Location | Role | Contribution |
|---|---|---|---|
| **Eik Schimmel, MD** | University Hospital, Technische Universität Dresden, Dresden, Germany | Author | Acquisition and analysis of data |
| **Hannah Fuhrer, MD** | University of Freiburg, Freiburg, Germany | Author | Acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Christine Fahrendorf, MD** | St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany | Author | Acquisition and analysis of data |
| **Anke Alberty, MD** | Kliniken Maria Hilf GmbH Mönchengladbach, Mönchengladbach, Germany | Author | Acquisition and analysis of data |
| **Jan Zinke, MD** | Jena University Hospital, Jena, Germany | Author | Acquisition and analysis of data |
| **Andreas Meisel, MD** | Charité–Universitätsmedizin Berlin, Berlin | Author | Conception and design of the study, acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |
| **Christian Dohmen, MD** | University of Cologne, Cologne, Germany | Author | Conception and design of the study, drafting or revising a significant portion of the manuscript or figures |
| **Henning R. Stetefeld, MD** | University of Cologne, Cologne, Germany | Author | Conception and design of the study, acquisition and analysis of data, drafting or revising a significant portion of the manuscript or figures |

## Appendix 2 Coinvestigators

| Name | Location | Role | Contribution |
|---|---|---|---|
| **Kornelius Fuchs, MD** | Department of Neurology, University Medical Center Regensburg | Coinvestigator | Data acquisition, supervision of personnel |
| **Berthold Schalke, MD** | | Coinvestigator | Data acquisition, supervision of personnel |

## Appendix 2 *(continued)*

| Name | Location | Role | Contribution |
|---|---|---|---|
| **Izabela Brachaczek** | Charité–Universitätsmedizin Berlin, Department of Neurology, NeuroCure Clinical Research Center | Coinvestigator | Data acquisition |
| **Jana Maidhof** | | Coinvestigator | Data acquisition |
| **Arno Wenke, MD** | | Coinvestigator | Data acquisition, supervision of personnel |
| **Manuel Hagen, MD** | Department of Neurology, University Hospital Erlangen | Coinvestigator | Data acquisition |
| **Jan Rahmig, MD** | Department of Neurology, University Hospital, Technische Universität Dresden | Coinvestigator | Data acquisition |
| **Wolf Niesen, MD** | Department of Neurology, University of Freiburg | Coinvestigator | Data acquisition, supervision of personnel |
| **Ingo Kleiter, MD** | Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum | Coinvestigator | Data acquisition, supervision of personnel |

## References


1. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. Neurology 2009;72:1548–1554.
2. Thomas CE, Mayer SA, Swarup R, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. Neurology 1997;48:1253–1260.
3. Spillane J, Hirsch NP, Kullmann DM, Taylor C, Howard RS. Myasthenia gravis: treatment of acute severe exacerbations in the intensive care unit results in a favourable long-term prognosis. Eur J Neurol 2014;21:171–173.
4. Ramos-Fransi A, Rojas-García R, Segovia S, et al. Myasthenia gravis: descriptive analysis of life-threatening events in a recent nationwide registry. Eur J Neurol 2015;22:1056–1061.
5. O'Riordan JI, Miller DH, Mottershead JP, Hirsch NP, Howard RS. The management and outcome of patients with myasthenia gravis treated acutely in a neurological intensive care unit. Eur J Neurol 1998;5:137–142.
6. Kalita J, Kohat AK, Misra UK. Predictors of outcome of myasthenic crisis. Neurol Sci 2014;35:1109–1114.
7. Werneck LC, Scola RH, Germiniani FMB, Comerlato EA, Cunha FMB. Myasthenic crisis: report of 24 cases. Arq Neuropsiquiatr 2002;60:519–524.
8. Damian MS, Ben-Shlomo Y, Howard R, et al. The effect of secular trends and specialist neurocritical care on mortality for patients with intracerebral haemorrhage, myasthenia gravis and Guillain-Barré syndrome admitted to critical care: an analysis of the Intensive Care National Audit & Research. Intens Care Med 2013;39:1405–1412.
9. Berrouschot J, Baumann I, Kalischewski P, Sterker M, Schneider D. Therapy of myasthenic crisis. Crit Care Med 1997;25:1228–1235.
10. Wong YS, Ong CT, Sung SF, et al. Clinical profile and outcome of myasthenic crisis in central Taiwan. Acta Neurol Taiwan 2016;25:129–135.
11. Murthy JMK, Meena AK, Chowdary GVS, Naryanan JT. Myasthenic crisis: clinical features, complications and mortality. Neurol India 2005;53:37–40; discussion 40.
12. Liu C, Wang Q, Qiu Z, et al. Analysis of mortality and related factors in 2195 adult myasthenia gravis patients in a 10-year follow-up study. Neurol India 2017;65:518–524.
13. Alkhawajah NM, Oger J. Late-onset myasthenia gravis: a review when incidence in older adults keeps increasing. Muscle Nerve 2013;48:705–710.
14. Hellmann MA, Mosberg-Galili R, Steiner I. Myasthenia gravis in the elderly. J Neurol Sci 2013;325:1–5.
15. Aragonès J, Bolíbar M, Bonfill M. Myasthenia gravis: a higher than expected incidence in the elderly. Neurology 2003;60:1024–1026.
16. Wu JY, Kuo PH, Fan PC, Wu HD, Shih FY, Yang PC. The role of non-invasive ventilation and factors predicting extubation outcome in myasthenic crisis. Neurocrit Care 2009;10:35–42.

17. Seneviratne J, Mandrekar J, Wijdicks EFM, Rabinstein AA. Noninvasive ventilation in myasthenic crisis. Arch Neurol 2008;65:54–58.
18. Rabinstein A, Wijdicks EFM. BiPAP in acute respiratory failure due to myasthenic crisis may prevent intubation. Neurology 2002;59:1647–1649.
19. Wiendl H. Diagnostik und Therapie der Myasthenia gravis und des Lambert-Eaton-Syndroms Die wichtigsten Empfehlungen auf einen Blick Definition und Klassifikation. DGN Leitlinien 2012:1–29.
20. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 2009;8:475–490.
21. Liu Z, Yao S, Zhou Q, et al. Predictors of extubation outcomes following myasthenic crisis. J Int Med Res 2016;44:1524–1533.
22. Seneviratne J, Mandrekar J, Wijdicks EFM, Rabinstein AA. Predictors of extubation failure in myasthenic crisis. Arch Neurol 2008;65:929–933.
23. Köhler W, Bucka C, Klingel R. A randomized and controlled study comparing immunoadsorption and plasma exchange in myasthenic crisis. J Clin Apher 2011;26:347–355.
24. Schneider-Gold C, Krenzer M, Klinker E, et al. Immunoadsorption versus plasma exchange versus combination for treatment of myasthenic deterioration. Ther Adv Neurol Disord 2016;9:297–303.
25. Drachman DB. Myasthenia gravis. N Engl J Med 1994;330:1797–1810.
26. Melzer N, Ruck T, Fuhr P, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. J Neurol 2016;263:1473–1494.
27. Cohen MS, Younger D. Aspects of the natural history of myasthenia gravis: crisis and death. Ann NY Acad Sci 1981;377:670–677.
28. Gajdos P, Chevret S, Toyka K. Plasma exchange for myasthenia gravis. Cochrane Database Syst Rev 2002;4:CD002275.
29. Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 2008;1:CD002277.
30. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology 2011;76:2017–2023.
31. Mandawat A, Kaminski HJ, Cutter G, Katirji B, Alshekhlee A. Comparative analysis of therapeutic options used for myasthenia gravis. Ann Neurol 2010;68:797–805.
32. Wendell LC, Levine JM. Myasthenic crisis. Neurohospitalist 2011;1:16–22.
33. Rabinstein AA. Noninvasive ventilation for neuromuscular respiratory failure: when to use and when to avoid. Curr Opin Crit Care 2016;22:94–99.

# Disputes & Debates: Editors' Choice

**Steven Galetta**, MD, FAAN, Section Editor

## Editors' note: Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain

In the article "Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain," Dr. Galhardoni et al. compared the analgesic effects of repetitive transcranial magnetic stimulation (rTMS) of the anterior cingulate cortex (ACC) or the posterior superior insula (PSI) against sham deep rTMS in 98 patients with central neuropathic pain (CNP) after stroke or spinal cord injury in a randomized, double-blinded, sham-controlled, 3-arm parallel study. They found that ACC- and PSI-rTMS were not different from sham-rTMS for pain relief despite a significant increase in heat thresholds after insular stimulation and anxiolytic effects after ACC-rTMS and concluded that different dimensions of pain can be modulated noninvasively by directly stimulating deeper structures without necessarily improving clinical pain. In response, Dr. Zugaib et al. point to their recent work suggesting that PSI-/ACC-rTMS involves more intense stimulation of superficial structures. They argue that the use of linear projection to estimate the stimulation targets—as was the case in the trial—does not correspond to the region of maximum-induced electrical field, which is more superficial, and therefore caution against interpreting the clinical findings as resulting from the stimulation of deep structures as opposed to a combination of stronger superficial and deeper stimulation. They suggest using electric field modeling to guide the coil positioning and adjustment of stimulation intensity. Responding to these comments, Dr. de Andrade et al. defend the precision of their approach, noting that in addition to linear projection-guided PSI stimulation providing antinociceptive effects in patients with CNP and healthy volunteers, direct cortical stimulation of the PSI during stereo-EEG in a previous study showed the same heat-pain changes as described by linear projection-target deep TMS. They also note that stimulation intensity was calculated using the tibialis anterior muscle as a parameter, represented medially in the primary motor cortex, suggesting that a measurable current was likely delivered to the PSI. They argue that computing electric fields would not solve the issue of stimulation intensity, and instead propose that future field models should account for the data from linear projection, validated against sham and active controls, in their algorithms. This exchange highlights the important points of debate in the field of rTMS regarding the most reliable means of targeting deeper structures in the brain, and conversely, identifying the responsible structural mediators of observed stimulation effects.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
*Neurology*® 2020;94:720. doi:10.1212/WNL.0000000000009302

## Reader response: Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain

João Zugaib (Ilhéus, Brazil), Janine R. Camatti (Santo André, Brazil), and Victor Hugo Souza (Espoo, Finland)
*Neurology*® 2020;94:720–721. doi:10.1212/WNL.0000000000009303

Galhardoni et al.[1] evaluated the effect of repetitive transcranial magnetic stimulation (rTMS) on the anterior cingulate cortex (ACC) and posterior superior insula (PSI) of patients with central

Author disclosures are available upon request (journal@neurology.org).

neuropathic pain (CNP). Multidimensional aspects of pain were evaluated with psychophysical tests, electrophysiologic recordings, and scales. rTMS in PSI increased the threshold for heat pain, whereas in ACC improved anxiety scores. It is plausible that the neuromodulation of these structures has a therapeutic potential for CNP.[2] On the other hand, we recently pointed out that rTMS over PSI and ACC involve greater stimulation of superficial rather than deeper structures.[3] In addition, estimation of the stimulation targets was based on a linear projection from the center of the coil.[4] Linear projection does not correspond to the region of maximum induced electric field on internally folded cortical structures, which is always on the more superficial tissue[5]; therefore, the clinical findings should not be regarded as the resultant of deep structures' stimulation instead of an ensemble of stronger spread superficial stimulation combined with deeper stimulation. Accordingly, electric field modeling may be used to guide the coil positioning and adjustment of stimulation intensity to achieve a significant pain relief. Certainly, there is great importance in the development of new therapeutic strategies for CNP.


1. Galhardoni R, Aparecida da Silva V, García-Larrea L, et al. Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain. Neurology 2019;92:e2165–e2175.
2. Peyron R, Fauchon C. The posterior insular-opercular cortex: an access to the brain networks of thermosensory and nociceptive processes? Neurosci Lett 2019;702:34–39.
3. Zugaib J, Souza VH. Transcranial magnetic stimulation for neuromodulation of the operculo-insular cortex in humans. J Physiol 2019; 597:677–678.
4. Hagiwara K, Isnard J, Peyron R, Garcia-Larrea L. Theta-burst-induced seizures reported by Lenoir et al: anterior or posterior insular seizures? Brain Stimul 2019;12:200–201.
5. Deng ZD, Lisanby SH, Peterchev AV. Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimul 2013;6:1–13.




## Author response: Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain

Daniel Ciampi de Andrade (São Paulo, Brazil), Ricardo Galhardoni (São Paulo, Brazil), Valquíria Aparecida da Silva (São Paulo, Brazil), Luís García-Larrea (Lyon, France), Camila Dale (São Paulo, Brazil), Abrahão F. Baptista (Santo André, Brazil), Luciana Mendonça Barbosa (São Paulo, Brazil), Luciana Mendes Bahia Menezes (São Paulo, Brazil), Silvia R.D.T. de Siqueira (São Paulo, Brazil), Fernanda Valério (São Paulo, Brazil), Jefferson Rosi (São Paulo, Brazil), Antonia Lilian de Lima Rodrigues (São Paulo, Brazil), Diego Toledo Reis Mendes Fernandes (São Paulo, Brazil), Priscila Mara Lorencini Selingardi (São Paulo, Brazil), Marco Antônio Marcolin (São Paulo, Brazil), Fábio Luís de Souza Duran (São Paulo, Brazil), Carla Rachel Ono (São Paulo, Brazil), Leandro Tavares Lucato (São Paulo, Brazil), Ana Mércia B. L. Fernandes (São Paulo, Brazil), Fábio E. F. da Silva (São Paulo, Brazil), Lin T. Yeng (São Paulo, Brazil), André R. Brunoni (São Paulo, Brazil), Carlos A. Buchpiguel (São Paulo, Brazil), and Manoel J. Teixeira (São Paulo, Brazil)
*Neurology*® 2020;94:721–722. doi:10.1212/WNL.0000000000009304

We thank Dr. Zugaib et al. for the interest in our work.[1] It has been suggested that modeling electric fields within the deep cortical structures would provide more reliable, target-effect conclusions. So far, the use of linear projection to target[1] the posterior superior insula (PSI) has provided antinociceptive effects as measured by increases in the heat-pain threshold in patients with central pain[2] and in healthy volunteers.[3o] Importantly, in a unique study,[4] direct cortical stimulation of the PSI during stereo-EEG showed exactly[4] the same heat-pain changes described by the linear projection-targeted deep transcranial magnetic stimulation (TMS). Taken together, these are very strong arguments for the precision of such an approach. In addition, in the setups cited above, stimulation intensity was calculated using the anterior tibialis muscle as a parameter (with the leg representation buried medially within the primary motor cortex), which attests that a measurable amount of induced electric current was indeed delivered to the PSI. As pointed out by Zugaib and Souza,[5] computing electric field would not solve the issue of intensity of stimulation. Because the linear projection-based deep TMS approach proved itself accurate on

Author disclosures are available upon request (journal@neurology.org).

psychophysical terms, we propose a pragmatic "reverse-modeling" perspective that future electric-field models should take into account the data from linear projection in their algorithms because they have been validated against sham and active controls and provided information on the intensity of stimulation all at once.


1. Ciampi de Andrade D, Galhardoni R, Pinto LF, et al. Into the island: a new technique of non-invasive cortical stimulation of the insula. Neurophysiol Clin 2012;42:363–368.
2. Galhardoni R, Aparecida da Silva V, García-Larrea L, et al. Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain. Neurology 2019;92:e2165–e2175.
3. Lenoir C, Algoet M, Mouraux A. Deep continuous theta burst stimulation of the operculo-insular cortex selectively affects Aδ-fibre heat pain. J Physiol 2018;596:4767–4787.
4. Denis DJ, Marouf R, Rainville P, Bouthillier A, Nguyen DK. Effects of insular stimulation on thermal nociception. Eur J Pain 2016;20:800–810.
5. Zugaib J, Souza VH. Transcranial magnetic stimulation for neuromodulation of the operculo-insular cortex in humans. J Physiol 2019;597:677–678.




## Editors' note: Clinical manifestations of homozygote allele carriers in Huntington disease

In the article "Clinical manifestations of homozygote allele carriers in Huntington disease", Dr. Cubo et al. examined the phenotypic differences between patients who were homozygous for Huntington disease (HD)—with both alleles carrying ≥36 CAG repeats—and those who were heterozygous with only one allele carrying such repeats, in 10,921 participants with HD in an international, longitudinal, case-control study (European Huntington's Disease Network Registry database). They found that homozygotes were infrequent (0.3%) and that the age at onset, HD phenotype, and disease progression did not differ significantly between homozygotes and heterozygotes. In response, Dr. Da Prat et al. noted a previous study that reported a more severe and rapid progression in homozygotes. They suggest using the term biallelic HD to refer to these patients to acknowledge the differences in the number of repeats that may exist between the 2 expanded alleles and cite a previous abstract from their group that also reported no differences in age at onset, cognition, motor capabilities, or disease evolution between a small sample of 7 patients with biallelic HD and heterozygous patients. Responding to these comments, Drs. Ramos-Arroyo and Cubo highlighted the potential drawbacks of using the term biallelic HD, noting the differences between patients with 2 expanded alleles carrying ≥36 CAG repeats vs those with one intermediate allele (27–35 repeats) who may have later-onset disease (both groups are combined under the biallelic definition), and noting the exclusion of compound heterozygotes with 2 nonfully penetrant repeat expansions from the conventional biallelic definition. They argue that these issues lead to imprecise categorization of patients with HD and potential noise in the analysis of clinical effects. This exchange illustrates the potential challenges that can arise in the interpretation of genotypic-phenotypic correlation studies from the use of what may appear at the first glance to be superficially discrepant definitions.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
*Neurology*® 2020;94:722. doi:10.1212/WNL.0000000000009305

Author disclosures are available upon request (journal@neurology.org).

# Reader response: Clinical manifestations of homozygote allele carriers in Huntington disease

Gustavo Da Prat (Buenos Aires), Jose Luis Etcheverry (Buenos Aires), Martin Cesarini (Buenos Aires), and Emilia Gatto (Buenos Aires)
*Neurology*® 2020;94:723. doi:10.1212/WNL.0000000000009307

We read with interest the article by Cubo et al.[1] Patients with homozygous Huntington disease (HD) are rare—considering a patient as homozygous when presenting with repetitions greater than 36 in both alleles. Differences in age at onset, clinical characteristics, and evolution have been hypothesized because the gain function of the mutation is due to both alleles. Nevertheless, it has been shown that these patients have a similar clinical evolution. However, a very early study conducted by Squitieri et al.[2] reported a more severe and rapid progression in homozygotes.

The term biallelic HD (B-HD) was introduced to describe those individuals with 1 mutated allele (≥40 CAG repeats) and one with ≥27 CAG repeats to differentiate them from individuals with 2 identical CAG repeats (true homozygous) or 1 fully expanded heterozygous (≥40 CAG repeats) allele. For this reason, we suggest the categorization of B-HD instead of "homozygous," as a more appropriate nomenclature.[3]

In our database, we identified 7 patients with B-HD among 150 patients with HD from June 2003 to May 2019. Coinciding with Cubo et al.,[1] we found no differences regarding the age at onset, cognition, motor capabilities, or disease evolution in patients with B-HD compared with the heterozygous patients with HD.[4]

1. Cubo E, Martinez-Horta SI, Santalo FS, et al. Clinical manifestations of homozygote allele carriers in Huntington disease. Neurology 2019;92:e2101–e2108.
2. Squitieri F, Gellera C, Cannella M, et al. Homozygosity for CAG mutation in Huntington disease is associated with a more severe clinical course. Brain 2003;126:946–955.
3. Uhlmann WR, Peñaherrera MS, Robinson WP, Milunsky JM, Nicholson JM, Albin RL. Biallelic mutations in huntington disease: a new case with just one affected parent, review of the literature and terminology. Am J Med Genet A 2015;167A:1152–1160.
4. Cesarini M, Parisi V, Persi G, et al. A retrospective analysis of clinical forms and age of onset of biallelic Huntington disease patients from an Argentinean Center [abstract]. Mov Disord 2017;32. Available at: mdsabstracts.org/abstract/a-retrospective-analysis-of-clinical-forms-and-age-of-onset-of-biallelic-huntington-disease-patients-from-an-argentinean-center/. Accessed May 3, 2019.



# Author response: Clinical manifestations of homozygote allele carriers in Huntington disease

Maria A. Ramos-Arroyo (Pamplona, Spain) and Esther Cubo (Burgos, Spain)
*Neurology*® 2020;94:723–724. doi:10.1212/WNL.0000000000009308

We appreciate the comments of Da Prat et al. comparing the results of our study[1] with their conclusions on the assessment of additional cases with 2 expanded HTT gene copies.[2]

Regarding terminology, we agree that "biallelic HD/mutations/expansions" might be an alternative term for the carriers of 2 expanded HTT alleles. By definition, biallelic carriers have a mutation in both maternal and paternal gene copies. For Huntington disease (HD), it could, therefore, include homozygotes for a particular CAG expansion and compound heterozygotes, carrying 2 different pathogenic alleles.

However, the term biallelic HD, as defined by Da Prat et al., presents, in our opinion, some major drawbacks. First, it is not useful in the analysis of genotype/phenotype relationships of the carriers

Author disclosures are available upon request (journal@neurology.org).

with 1 and 2 expanded (≤36 CAGs) HTT copies (homozygotes and compound heterozygotes), as in our study.[1] Second, sequences of 27–35 CAG repeats are considered mutated/expanded alleles. We and others have observed that intermediate alleles (IAs) might confer late-onset abnormal motor and/or cognitive phenotype.[3] However, at present, IAs are considered unstable but are seen as non-HD–causing alleles.[4] Thus, their inclusion in the mutation range of the HTT gene seems premature and confusing. Third, the term excludes the compound heterozygotes in patients with HD carrying 2 nonfully penetrant CAG repeats.

In conclusion, we think that the term biallelic mutations leads to imprecision in grouping and categorization of patients with HD, adding "noise" to the analysis of their clinical effects. In fact, it has not been previously used in other diseases caused by repeat expansion mutations.


1. Cubo E, Martinez-Horta SI, Santalo FS, et al. Clinical manifestations of homozygote allele carriers in Huntington disease. Neurology 2019;92:e2101–e2108.
2. Cesarini M, Parisi V, Persi G, et al. A retrospective analysis of clinical forms and age of onset of biallelic Huntington disease patients from an Argentinean Center. Mov Disord 2017;32(suppl 2). Abstract.
3. Cubo E, Ramos-Arroyo MA, Martinez-Horta S, et al. Clinical manifestations of intermediate allele carriers in Huntington disease. Neurology 2016;87:571–578.
4. Caron NS, Wright GEB, Hayden MR. Huntington disease. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReview® [Internet]. Seattle: University of Washington; 1998:1993–2019. Updated 2018 Jul 5.




CORRECTIONS

## Myasthenic crisis demanding mechanical ventilation: A multicenter analysis of 250 cases

*Neurology*® 2020;94:724. doi:10.1212/WNL.0000000000009262

In the Clinical/Scientific Note "Myasthenic crisis demanding mechanical ventilation: A multicenter analysis of 250 cases" by Neumann et al.,[1] Dr. Schneider's first name should be listed as Hauke. The authors regret the error.

### Reference


1. Neumann B, Angstwurm K, Mergenthaler P, et al. Myasthenic crisis demanding mechanical ventilation: a multicenter analysis of 250 cases. Neurology 2020;94:e299–e313.


## Teaching Video NeuroImages: Slow periodic myoclonus in subacute sclerosing panencephalitis and fulminant Wilson disease

*Neurology*® 2020;94:724. doi:10.1212/WNL.0000000000009393

In the article "Teaching Video NeuroImages: Slow periodic myoclonus in subacute sclerosing panencephalitis and fulminant Wilson disease" by Meza et al.,[1] the videos should be swapped so that the first video corresponds with the second legend and vice versa. The authors regret the errors.

### Reference


1. Meza RM, Schulz H, Correa J, et al. Teaching Video NeuroImages: Slow periodic myoclonus in subacute sclerosing panencephalitis and fulminant Wilson disease. Neurology 2019;93:e1410–e1411.


Author disclosures are available upon request (journal@neurology.org).