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Case Report

MYASTHENIA CRISIS VS CHOLINERGIC CRISIS: CHALLENGES IN CRISIS MANAGEMENT WITHOUT PLASMAPHERESIS OR INTRAVENOUS IMMUNOGLOBULIN (IVIG)

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ABSTRACT

Introduction: Myasthenia gravis (MG) is an acquired autoimmune disease that clinically characterized by weakness & fatigability exertion in skeletal muscle with prevalence as high as 2–7 in 10,000 and women are affected more frequently than men (~3:2). Over 12-16% of generalized MG patients experience crisis once in their lifetime. Respiratory failure is a serious complication of myasthenia gravis that may be caused by an exacerbation of myasthenia (myasthenia crisis) or an excess treatment of a cholinesterase inhibitor (cholinergic crisis). **Case Report:** Thirty-two years old woman refereed from a private hospital to ED for further treatment with myasthenia in crisis, after nine days of treatment in the previous ICU. Patient already in intubation with mechanical ventilation and history of the treatment of high dose of multiple anticholinesterase drug and steroid without plasmapheresis or immunoglobulin intravenous. During admission, diarrhea was present, with no sign of GI infection. On the third day of admission, the patient performed Spontaneous Breathing Trial and was a success then extubated. Then two day after extubation, the patient falls to respiratory failure and need mechanical ventilation. Anticholinesterase test was performed, and it shows no improvement in clinical signs, and diagnose as Cholinergic Crisis. After re-adjustment of anticholinesterase drug with a lower dose, clinically, the respiratory condition improved, and on the 10th day of admission, the patient was succeed extubated. At 12nd days of ICU admission, patient discharge from ICU. **Discussion:** Myasthenia and Cholinergic Crisis is a life-threatening condition that characterized by generalized respiratory muscle weakness that requires ventilatory support. Respiratory failure may be present in cholinergic crisis without cholinergic symptoms, such as miosis, diarrhea, urinary incontinence, bradycardia, emesis, lacrimation, or salivation. The most important management aspect of Myasthenia patients in crisis is the recognition and treatment of myasthenia vs cholinergic crisis.

Keyword: Myasthenia Crisis; Cholinergic Crisis; Plasmapheresis; Intravenous Immunoglobulin; Anticholinesterase Inhibitors

ABSTRAK

Pendahulun: Myasthenia gravis (MG) adalah gangguan kelemahan otot lurik karena aktifitas yang disebabkan kelainan autoimun dengan prevalensi 2-7 kasus tiap 10.000 orang dan lebih sering terjadi pada wanita (3:2). Sekitar 12-16% pasien MG akan mengalami minimal 1 kali periode krisis, yang merupakan komplikasi berbahaya yang menyebabkan gagal napas. Kondisi ini dapat terjadi karena adanya memburuknya MG (krisis Miastenia) atau *overdose* obat *cholinesterase inhibitor* (Krisis Cholinergik). **Case Report:** Wanita 32 tahun rujukan dari ICU RS Swasta dengan krisis miastenia untuk perawatan lanjutan setelah perawatan 9 hari. Pasien dengan Ventilator dan riwayat penggunaan berbagai jenis obat *anticholinesterase inhibitor* dosis tinggi dan steroid. Saat di UGD, pasien mengalami diare tanpa ada tanda-tanda infeksi saluran cerna. Pada hari ketiga perawatan ICU, pasien dapat lepas dari Ventilator setelah berhasi dilakukan *spontaneous breathing trial*. Namun dua hari setelah ekstubasi, pasien kembali mengalami gagal napas dan dilakukan intubasi ulang. Tes anticholinergic dilakukan dengan hasil mengarah pada krisis cholinergic. Setelah pengaturan ulang dosis obat anticholinesterase, kondisi klinis membaik dan pada hari ke-10 pasien lepas dari ventilator. Pasien pindah dari ICU setelah 12 hari perawatan. **Diskusi:** Krisis Miastenia – Cholinergik (KMC) adalah kondisi *life threatening* yang ditandai oleh kelemahan otot pernapasan yang menjadi gagal napas. Gagal napas pada krisis cholinergic dapat terjadi meskipun tidak diikuti oleh tanda atau gejala cholinergic yang lain (miosis, Diare, Inkontinesia urin, bradikardi, emesis, atau salivasi). Penatalaksanaan paling penting pada pasien miastenia pada kondisi krisis adalah identifikasi dan penanganan awal pada KMC.

Kata Kunci: Krisis Myastenia; Krisis Kolinergik; *Plasmapheresis*; *Intravenous Immunoglobulin*; *Anticholinesterase Inhibitor*

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INTRODUCTION

Myasthenia crisis is a myasthenia gravis' (MG) complication that characterized by worsening of skeletal muscle weakness which is resulting in respiratory failure that requires intubation and mechanical ventilation. (1) The cholinergic crisis is an emergency that is mainly characterized by flaccid paralysis and respiratory failure, which mainly occurs due to improper administration or intake of anticholinergic agents in MG patients. (2) The worldwide incidents are about 8 to 20 cases per 100,000 people. (3) Crisis periods occur on 15-20% of myasthenia patients, at least once in their lives. First crisis occurs on 8-12 months from onset of MG with 5% mortality rate. (1)(4)

In the last three to four decades the use of cholinesterase inhibitors drug has been less in moderate to severe and/or crisis, certainly not as a single treatment. Because cholinesterase inhibitors may have a different half-life in critically ill patients which resulting in absorption decreasing of enteral formulations. Increased weakness and interference with extubation may be lead by overdose of these drugs with the resulting incident of cholinergic crisis with or without other cholinergic symptoms. (5)(6) Plasmapheresis or Intravenous Immunoglobulin (IVIg) is the gold standard of MG therapy in crisis, and most guidelines not recommended continuity of cholinesterase inhibitors during the crisis. (3)-(5)(6)

CASE REPORT

Thirty-two years old woman refereed from a private hospital to ED for further treatment with myasthenia in crisis and suspect pneumonia, after nine days of treatment in the previous ICU. Patient already in intubation with mechanical ventilation (MV) and history of the treatment of high dose of multiple anticholinesterase drug, Pyridostigmine oral 60mg every 4 hours, Neostigmine iv. 0,5mg every 8 hours and steroid, methylprednisolone iv 62,5mg every 8 hours, without plasmapheresis, IVIg, or another immunosuppressant. The patient diagnoses with MG for 3 years with routine daily pyridostigmine oral without dose adjustment by a physician. A week before admission on the previous ICU, the patient got common cold for three days and a general weakness that resulting in dyspnea needed for MV.

During admission at Emergency Department, Dr. Soetomo General Academic Hospital, patient with Glasgow coma scale (GCS) E4 Mx V6 (with endotracheal tube), stable vital sign, assisted respiration with slight rhonchi in a small area in both lung and from muscle strength grading examination, superior and inferior extremity got scale 5 out of 5 and 2-4 out of 5 with mean motoric strength grade were 4 out of 5. Other signs and symptoms are diarrhea without signs of intestinal infection. Form laboratory (Table 1) and radiology examination (figure 1), there are increased white blood count and liver function test with other normal blood laboratory and normal chest x-ray.

Diarrhea still present for the first two days of treatment in ICU and muscle weakness getting worse with mean extremity motoric strength grade was below 3 out of 5. Pyridostigmine dose were reduced to 60 mg every 8 hours. The next day evaluation, diarrhea has already stopped but there is no improvement on muscle strength scale, so based on clinical judgment, the dose of

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pyridostigmine was increased into double dose (60 mg every 4 hours). After increasing dose, muscle strength grade was increased and the spontaneous breathing trial was performed successfully.

Tabel 1. Routine Laboratory Result at Emergency Department

Laboratory examination	Value
Hemoglobin	15,9 g/dL
Haematocrit	47 %
White Blood Count	19.900 x 10^9/L
Blood Sugar	132 mg/dL
SGOT	45 U/L
SGPT	208 U/L
Urea	15mg/dL
Creatine	0,54 U/L
Natrium	140 mmol/L
Kalium	4,66 mmol/L
Chloride	93 mmol/L

Pyridostigmine dose was re-adjusted by reducing a half and the patient was extubated on the third day of ICU treatment. After 24 hours extubating, patient show tachypnea until 30-35 breath per-minute with a stable vital sign and without muscle weakness and any cholinergic sigh (such as hypersalivation, diarrhea, miosis, and hyper-lacrimation).

The anticholinergic test was performed by using neostigmine 0,5 mg iv. and the result was positive by decreased respiration rate until normal, then pyridostigmine dose was increased by 60 mg every 4 hours. Even though the PaO2/FiO2 ratio was 230 before the Anticholinergic test, the clinically respiration condition was getting better after the test, so the patient are not re-intubation for observation. But the next day, another tachypnea episode happened again with the patient unable to cough and fall to respiratory failure. This episode was followed by muscle weakness. The patient was re-intubate and pyridostigmine dose was increased twice as

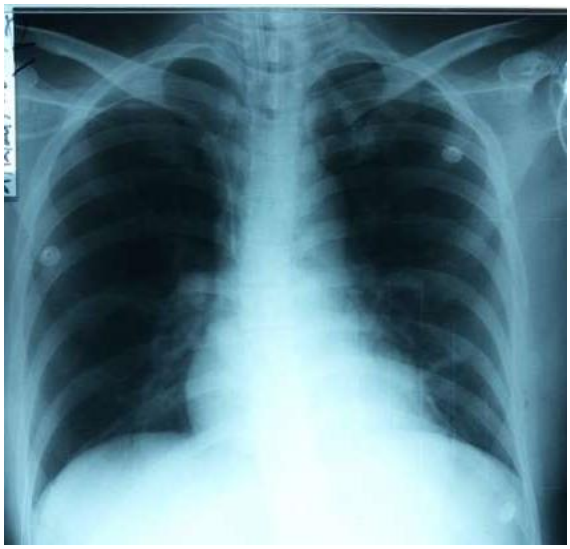

Figure 1. Chest X-ray at the Emergency Department. There is no sign of Pneumonia, normal Chest X-ray

before (120 mg every 4 hours). Chest X-ray after re-intubation shows sputum retention with a decrease of PaO2/FiO2 Ratio (288).

Re-adjustment dose was based on an anticholinergic test that performed the previous day, and no sign of cholinergic activity at all. After two days of re-intubate, muscle weakness was getting worse and still, there was no signs of cholinergic activity. Re-adjust pyridostigmine dose was doing by reducing it with the assumption it could be caused by the cholinergic crisis. We gradually decrease the dose, on the first day reduce to 60 mg every 4 hours, then every 8 hours. On the eighth to ninth days of ICU treatment or third to fourth days after re-intubate, muscle strength was increase and patient able to be wean from mechanical ventilation.

On the tenth days of ICU treatment, patients were extubated and pyridostigmine dose were adjusted slightly increased (60 mg every 6 hours) to prevent possible another myasthenia crisis (dose too low) with the precaution of cholinergic dose (dose too high).

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Evaluation after re-adjustment of anticholinesterase drug with a lower dose, clinically, respiratory condition, and muscle strength were improving (detail Figure 2).

Corticosteroids (CSs) therapy were given continually with methylprednisolone iv. 125 mg every 6 hours, and tapering down at ward. After the twelfth days of ICU treatment, patient discharge from ICU and move to neurology ward, and chest x-ray on the fifteenth days of hospital admission shows normal result.

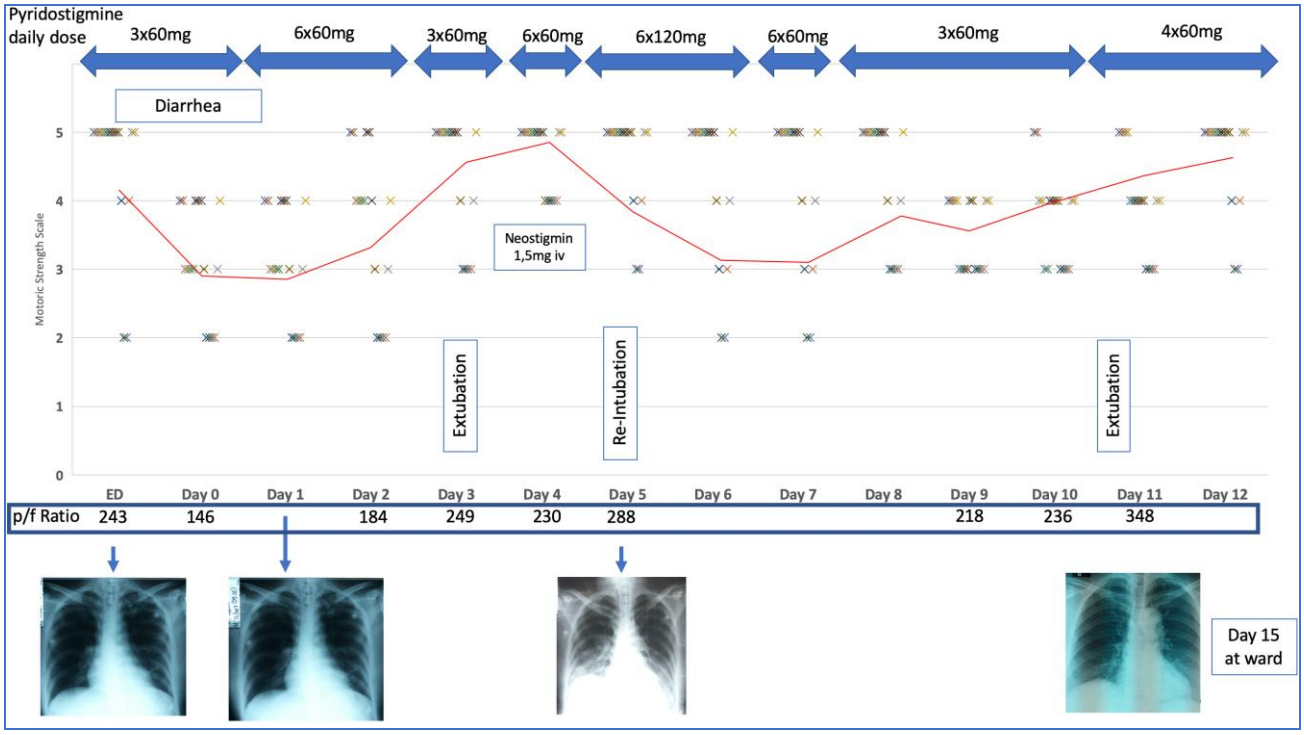

Figure 2. Progress of muscle strength, Pyridostigmine daily dose, PaO2/FiO2 ratio, Chest X-Ray during Hospital Admission

DISCUSSION

The pathogenesis of MG is the absent of acetylcholine receptors (AChRs) on the postsynaptic membrane of the neuromuscular junction (NMJ) because of the production of AChR and/or muscle-specific receptor tyrosine kinase (MuSK) antibodies (Abs), which as the result of the loss of postsynaptic AChRs and associated with NMH destruction. (8) Since the uses of corticosteroid (CSs) as MG treatment in the 1950s, Immunomodulating therapies, such as plasmapheresis, IVIg, and immunosuppressant, have replaced Acetylcholinesterase inhibitors (AChEIs) as sole therapies in crisis. (3)(5)(8)(9) AChEIs work as enzyme Acetylcholinesterase (AchE) competitive blockade in the extracellular matrix of the folded postsynaptic muscle endplate membrane. The result of these actions are the breaks down of Acetylcholine (ACh) into choline and acetate, the inactive metabolites of ACh. Pyridostigmine, that available in 60-mg tablets, is one of the most commonly used drug, which begins to work 30 minutes after oral administration and duration of action about 3-6 hours. (8)

AChEIs induce the corresponding adverse cholinergic effects on both muscarinic and nicotinic synapses, such as gastrointestinal

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tract hypermotility (e.g., abdominal pain, diarrhea, etc.), hyper-salivation and respiratory hyper-secretions, hyperhidrosis, and bradycardia or arrhythmia. Overtreatment of AChEIs may give rise to a serious cholinergic crisis (e.g., respiratory failure), which results from overactivity of neuromuscular transmission by excessive ACh.

The cholinergic crisis is uncommon because most of the guidelines suggest to stop AChEIs when crisis period occurs, but the cholinergic crisis is still an important evaluation of the patient in myasthenic crisis in received AChEIs treatment. (1)(8)(9) Randomized controlled trials in myasthenic crisis have been limited, perhaps because MG is a rare disease and difficult to recruit many suitable patients. Because of these reasons, most physicians have chosen immunotherapies that available within their medical environments and based on their own clinical experiences. (8)

Patients cannot be therapeutic with plasmapheresis or IVIg because they are not financially able and do not have insurance. So, even though at the crisis, the only option was AChEIs and corticosteroids (CSs). CSs are commonly used as the first-line drug as Immunosuppressants (IS). The reason using these drugs is for inducing comparatively rapid remission and bridging to long-term maintenance therapy using other ISs or immunomodulators until the onsite of these drugs. CSs are used in conjunction with AChEIs. High-dose methyl prednisolone may be initiated at the same time with AChEIs since the effect of methylprednisolone happens after 2 weeks. (1) The use of High-dose corticosteroids in MG patients should be performed with caution, as this drug can worsening of weakness in non-ventilated patients, around one-third of the cases. In the mechanical ventilated patient, the initiation or the escalation of these drugs should be considered. (10)

Tabel 2. Myasthenia Crisis versus Cholinergic Crisis

	Crisis	
	Myasthenia	**Cholinergic**
Focal or generalized muscle weakness	+	+
Respiratory difficulty or failure	+	+
Cholinergic symptoms and signs		
Diarrhea	-	+/-
Urinary Incontinentia	-	+/-
Miosis	-	+/-
Bronchospasm/Bronchorrhea	+/-	+/+
Bradycardia	-	+/-
Emesis	-	+/-
Salivation	-	+/-
Lacrimation	-	+/-
AChEIs Test	+	-

Source: Hetherington KA (6)

The most difficult part was recognizing and differentiating between Myasthenia Crisis (MC) versus Cholinergic Crisis (CC) (detail table 2). Both myasthenia and cholinergic crisis can be present as respiratory failure. Triggers for MC include disease exacerbations, noncompliance with AChEIs medication, adverse effects of other medications, fever, and emotional stress. CC is secondary to excess AChEIs. In these cases, Ach could over-stimulation of striated muscles at the NMJ, which results in flaccid muscle paralysis that can be clinically indistinguishable from weakness caused by MC.

Respiratory failure may be present in the cholinergic crisis without other cholinergic symptoms, such as miosis, diarrhea, urinary incontinence, bradycardia, emesis,

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lacrimation, or salivation. Therefore, as with all seriously ill patients, priority is given to establishing and maintaining an airway and assuring adequate breathing. The respiratory status of a patient with myasthenia or cholinergic crisis can worsen unpredictably. Close monitoring of the patient's respiratory status and dose adjusting of AChEIs are mandatory. (1)(4)(6)(11)

CONCLUSION

Both myasthenia and cholinergic crisis can be present as respiratory failure. Respiratory failure may be present in the cholinergic crisis without other cholinergic symptoms and signs. Close monitoring of the patient's respiratory status and dose adjusting of AChEIs are mandatory and challenging.

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