INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

2023 July; 29(3): 309 - 313
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

Therapeutic Plasma Exchange in Crisis Myasthenia Gravis with Pregnancy

Anak Agung Ayu Lydia Prawita, Ida Ayu Putri Wirawati, Sianny Herawati

Department of Clinical Pathology, Faculty of Medicine, Udayana University/Sanglah Hospital Denpasar, Indonesia. E-mail: gunglydia18@gmail.com

ABSTRACT

Myasthenic Crisis (MC) is a clinical diagnosis defined by respiratory failure in patients with Myasthenia Gravis (MG). As MG symptoms worsen, the weakness of the respiratory muscles or upper airway can increase so much that it causes difficulty swallowing or breathing, resulting in respiratory distress. One of the triggers for a myasthenic crisis is pregnancy. In this case, the patient was undergoing a second pregnancy with a gestational age of 28-29 weeks and had been diagnosed with MG 4 years ago. The female patient, 27 years old, had complaints of shortness of breath, difficulty chewing, and weakness in the extremities. During her stay in the hospital, the patient's condition worsened and she experienced a myasthenic crisis. Therapeutic Plasma Exchange (TPE) was administered to the patient 3 times and the patient's had clinical improvement. The patient was discharged with pyridostigmine and methylprednisolone therapy. Therapeutic plasma exchange is a safe and effective procedure for the management of myasthenia gravis during pregnancy. Prompt diagnosis and proper management can reduce morbidity in myasthenia gravis, especially those in crisis.

Keywords: Myasthenia gravis, myasthenic crisis, therapeutic plasma exchange

INTRODUCTION

Myasthenia Gravis (MG) is a relatively rare autoimmune disorder that happens to the neuromuscular junction (NMJ) and manifests as a weakness in particular muscles that get better with rest. Eighty-five percent of cases are caused by an antibody towards the acetylcholine receptors on the NMJ post-synapse side.[1] Myasthenia gravis is an autoimmune disease that can happen at any age. The incidence is around 1.7 to 21.3 per million people in the world. Myasthenia gravis is two times more common in female patients compared to male patients and usually happens in the third decade of life.[2] Therefore it is not uncommon during the patient's illness to undergo pregnancy. The initial manifestations of MG may occur during pregnancy or the postpartum period.

However, pregnancy and post-partum status have been reported as triggers that can exacerbate the disease. The course of MG is highly variable and unpredictable during pregnancy and also the clinical course in an earlier pregnancy does not predict the course of a subsequent pregnancy. Myasthenic crisis is defined as a constellation of clinical conditions in which within a few days, or more rarely, a few hours, there is severe weakness of bulbar-innervated muscles or the respiratory muscles, which restricts breathing or speech ability so severely that supportive feeding, intubation or ventilation are required. Myasthenic crises thus require hospitalization in a monitored intermediate care facility or intensive care unit. [3,4] Myasthenic crises are rare during pregnancy and can be a challenge in diagnosis and management because they are associated with physiological changes and limited treatment options. This is a case report about MG's crisis with pregnancy.

CASE

A-27-year-old female, with the main complaint of shortness of breath. The patient had difficulty breathing 2 days before admission. Shortness of breath worsens in the afternoon and was accompanied by coughing and a runny nose 4 days before hospitalization. The patient had difficulty chewing due to fatigue, causing the patient to only be able to eat soft food. The patient also complained of weakness in the extremities especially after repetitive movements and after standing for a long period. Fever was denied. The patient was currently in her second pregnancy. After admittance to the emergency room, the patient was hospitalized in the regular inpatient ward. A week after admittance, the patient's condition worsened, and respiratory failure

occurred causing the patient to be moved to the intensive care unit. The patient was first diagnosed with myasthenia gravis 4 years ago and got mestinon 5x60 mg and Methylprednisolone 3x12.5 mg. Physical examination showed that the patient was moderately ill, had a blood pressure of 90/60 mmHg, heart rate of 110 times per minute, temperature of 36.5°C, and respiratory rate of 22 times per minute. Complete blood count and hemostasis examination during hospitalization can be seen in Table 1.

Complete blood count and hemostasis examination show mild leukocytosis. Clinical chemistry results can be seen in Table 2.

Blood gas analysis showed various results. On admission the results were still within normal limits, after a couple of days, the patient's condition worsened and there were mixed acid-base disorders, respiratory and metabolic alkalosis, which can be seen in Table 3.

The patient was managed as follows; intensive care with intubation and ventilator attached, IVFD NaCl 0.9% 20 drops per minute, Methylprednisolone 125 mg every 8 hours intravenously, Lansoprazole 30 mg every 12 hours intravenously, Pyridostigmine 60

Table 1. Complete blood count dan hemostasis examination

Parameter	27/02/2020	04/03/2020	12/03/2020	Reference Range
WBC (10^3/µL)	13.22	17.91	10.71	4.1-11.0
RBC (10^6/µL)	3.32	3.97	3.52	4.0-5.2
HGB (g/dL)	8.75	9.57	8.85	12.0-16.0
HCT (%)	26.95	32.87	28.54	36.0-46.0
PLT (10µ/µL)	223.70	339.80	221.20	140-440
PPT (second)		12.5	13.6	10.8-14.4
INR (second)		0.89	0.97	0.9-1.1
APTT (second)		26.2	30.8	24-36
Fibrinogen (mg/dL)		389	304	140-450

Table 2. Clinical chemistry results

Parameter	27/02/2020	04/03/2020	07/03/2020	10/03/2020	12/03/2020	Reference Range
AST (U/L)	16.8					11 - 33
ALT (U/L)	6.10					11 - 50
Albumin (g/dL)	3.40		3.30	4.20	4.10	3.20 - 4.50
Random Blood Glucose (mg/dL)	103					70-140
BUN (mg/dL)	3.00		10.00			8.0-23.0
Creatinine (mg/dL)	0.38		0.22			0.70 - 1.20
Potassium (mmol/L)	3.09	3.20	2.99	3.92	4.09	3.50-5.10
Sodium (mmol/L)	136	139	141	142	139	136 - 145
Calcium (mg/dL)		8.5	8.2	9.0	9.2	8.80 - 10.2
Chloride (mmol/L)	108	110	106.6	100.6	101	94-110
Magnesium (mg/dL)		1.49	1.38	1.67	1.62	1.6 - 2.6
CRP (mg/L)	24.02					0.0 - 5.0

Table 3. Blood gas analysis results

Parameter	27/02/2020	02/03/2020	03/03/2020	07/03/2020	10/03/2020	11/03/2020	Reference Range
pH	7.41	7.48	7.47	7.46	7.36	7.45	7.35-7.45
pCO_2 (mmHg)	38.5	30.6	29.8	42.5	53.8	47.0	35.00-45.00
pO_2 (mmHg)	85.90	187.20	263.60	179.80	120.10	94.50	80.00-100.0
BEecf (mmol/L)	-0.6	5.7	-2.6	5.9	4.2	7.5	-2-2
HCO^{3-} (mmol/L)	24.00	29.30	21.10	29.70	29.70	31.60	22.00-26.00
SO_2c (%)	96.6	99.4	99.7	99.3	98.2	97.4	95%-100%
TCO_2 (mmol/L)	25.20	30.50	22.00	31.00	31.30	33.00	24.00-30.00

mg every 5 hours orally, performed Therapeutic Plasma Exchange (TPE) 3 times on March 6, 2020, March 10, 2020, and March 12, 2020. The patient was installed with a double lumen and needed 2580 mL of replacement fluid. For fluid replacement, 5% albumin and citrate dextrose (ACD) anticoagulant were used as anticoagulants. Three calcium supplement tablets were given before each procedure as prophylaxis for citrate poisoning and hypocalcemia. During the procedure, monitoring of the mother's blood pressure and fetal heart rate was carried out. After TPE, the patient returned for laboratory tests to determine the levels of hemoglobin, platelets, and electrolytes.

DISCUSSION

Myasthenia gravis is a neuromuscular disorder characterized by weakness and fatigue of the skeletal muscles. The neuromuscular abnormalities in MG are caused by an autoimmune response mediated by specific anti-AChR antibodies. Myasthenia gravis has a prevalence of 2-7 in 10,000 cases. Overall, females are affected more often than males with a ratio of 3:2. The main clinical features in MG are muscle weakness and fatigue. Muscle weakness increases with repeated use or at the end of the day and may improve after rest or sleep. Swallowing difficulties may occur as a result of muscle weakness of the palate, tongue, or pharynx, causing nasal regurgitation or aspiration of liquids or food. Extremity muscle weakness in MG is often proximal and may be asymmetric. Patients may also experience weakness in the respiratory muscles. The course of MG disease often varies. Exacerbations and remission may occur, especially during the first few years after the onset of the disease. Remissions are rarely complete or permanent. Infection or systemic disorders can cause an increase in myasthenic weakness and can trigger a crisis condition.[5,6] This patient complained of shortness of breath. Shortness of breath becomes more burdensome, especially in the afternoon. Shortness of breath was accompanied by cough and runny nose. The patient also complained of difficulty chewing due to fatigue causing the patient to only be able to eat soft foods. In addition, the patient complained of weakness in extremities when moving repeatedly and standing for a long time. The complaints felt by this patient are following the clinical picture of MG.

Classification according to The Medical Scientific Advisory Board (MSAB) of the Myasthenia Gravis Foundation of America (MGFA) divides MG into 5 main classes and several subclasses, as follows:[7] Class I: any ocular muscle weakness; may have weakness of eye closure. All other muscle strength normal; Class II: mild weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity; Class II A: predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles; Class II B: affecting oropharyngeal muscles, respiratory muscles, or both. Weakness in body muscles and axial muscles are lighter compared to class II A; Class III: severe weakness in ocular muscles, while other muscles experience moderate weakness; Class III A: predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles; Class III B: predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both; Class IV: severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity; Class IV A: predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles; Class IV B: predominantly affecting oropharyngeal, respiratory muscles, or both. It also has lesser or equal involvement of limb, axial muscles, or both. There can also be a weakness in the limbs, axial muscles, or both, there can also be the use of a feeding tube without intubation; Class V: is defined by intubation, with or without mechanical ventilation. In this case, the patient was diagnosed as MGFA V because the patient's condition had worsened, requiring intensive care with intubation and a ventilator.

Myasthenia gravis can have a significant impact on pregnancy. Several studies have shown a wide range of risks of MG exacerbation during pregnancy, ranging in individual series from 0% to 60%.[8] Exacerbations are more common in the first and third trimester of pregnancy, and 6-8 weeks after delivery, and less frequently in the second trimester.[9] The patient had been diagnosed with MG 4 years ago and the patient had another exacerbation in the third trimester of her pregnancy.

Laboratory tests used to help establish the diagnosis of myasthenia gravis are tests to detect the presence of autoantibodies. Other laboratory tests are used to help follow up with the patient during therapy. The diagnosis of MG should be made immediately, starting with testing for AChR, MuSK, or LRP-4 antibodies. If antibody testing is not performed, nerve conduction studies with repeated nerve stimulation or single fiber electromyography (EMG), which are more sensitive can be performed safely in pregnancy. In non-pregnant patients with

newly diagnosed MG with AChR antibodies, chest Computed Tomography (CT) should be performed to assess thymoma. However, in pregnant patients with MG, radiation exposure should be avoided and imaging of the thymus can generally be delayed until after pregnancy. In cases where there is a strong clinical suspicion of thymoma, chest Magnetic Resonance Imaging (MRI) is preferable to chest CT during pregnancy.[9] Complete blood count shows mild leukocytosis that can show a probability of infection or inflammation that is also supported by increased CRP levels. Hemostasis tests were within normal limits. Clinical chemistry results show a decrease in kidney function and electrolyte disturbances while blood gas analysis showed a mixed acid-base disorder as a result of the patient's autoimmune disease. In this case, antibody testing was not performed due to limited facilities.

Myasthenic crisis is a clinical diagnosis defined by respiratory failure in patients with MG. As MG symptoms worsen, weakness of the respiratory or upper airway muscles may increase causing difficulty to swallow or breathe, resulting in respiratory distress. A crisis occurs in 15-30% of patients with MG. Myasthenic crises can occur at any time in the course of the disease but are more common early after diagnosis (in the first 2–3 years, median 8 months). Almost any form of physical or emotional stress can trigger MC. Infection has been shown to cause >30% of MG crises, with respiratory infections being the most common. The crisis can also be precipitated by several other causes, including drugs, poor control of the underlying disease, pregnancy, surgery, acute fever, or even emotional disturbance.[1] Patient in this case was undergoing her second pregnancy at 28-29 weeks' gestation. A few days after the patient was admitted to the hospital, the patient's condition worsened and the patient experienced an MC because the patient had respiratory failure causing the patient to be transferred to the intensive care unit with intubation and a ventilator. In this case, pregnancy is the possibility to trigger the critical condition of this patient.

A myasthenic crisis occurs less frequently during pregnancy and presents unique management challenges due to physiological changes and limited treatment options.[5] Medical management aims to improve muscle function by increasing acetylcholine levels in the NMJ and by suppressing autoantibody production. When the muscle weakness is mild, no treatment is needed. The main treatment in MG includes drugs (pyridostigmine and neostigmine) with inhibit acetylcholinesterase enzyme for symptomatic relief as well as corticosteroids and alternate immunosuppressant drugs (methotrexate, azathioprine, mycophenolate, cyclosporine, cyclophosphamide as well as pulse intravenous immunoglobulins). Severe exacerbations or myasthenic crises require either plasma exchange or intravenous immunoglobulin with supportive care including ventilator support if required. [10,11] Patients are given corticosteroid therapy, namely Methylprednisolone, Pyridostigmine (Mestinon), Lansoprazole, and TPE.

The first-choice method for treating myasthenic crisis is plasma exchange. Treatment with 5–6 sessions is effective. An effect will be apparent within a few days.[4] Therapeutic plasma exchange is performed to lower AChR levels, although it has also been reported to be successful in 10% to 15% of symptomatic MG patients who have no detectable antibodies. Therapeutic plasma exchange is recommended for patients with MG who have severe symptoms such as impaired respiratory, swallowing, and locomotion functions, and to prepare patients for thymectomy or surgery. Therapeutic plasma exchange may consist of 1 to 1.5-volume plasma exchanges performed daily for 5 to 6 days. Patients with stable chronic disease who have mild exacerbations can be treated with 2-3 times TPE per month. Therapy should be tailored to the needs of the patient. Five percent albumin is used as a replacement fluid.[12]

Pregnancy causes several physiological changes that can affect the effectiveness and risks of TPE. Blood volume must be calculated to compensate for changes associated with pregnancy. Reports of TPE for pregnant patients have been largely limited to isolated cases in which patients had an autoimmune-type disease that had failed other treatment modalities. However, technical details regarding the appropriate volume and fluid exchange, as well as a description of the potential complications for TPE in pregnant patients are lacking. In addition, several publications also state that TPE is generally considered safe in pregnant patients and provide recommendations that pregnant patients who will undergo TPE be positioned in the left lateral decubitus to minimize the effect of the uterus pressing on the inferior vena cava, which can cause hypotension. Some recommendations that must be considered and become a routine part of all TPE procedures are shown in Table 4.[13]

In this case, TPE was performed 3 times on March 6th, 2020, March 10th, 2020, and March 12th, 2020. The patient's position at the time of the procedure was

Table 4. Recommendations for performing TPE in pregnant patients

Recommendation	Reason
Left lateral decubitus position	Positioning the patient in the left lateral decubitus position will help minimalize the inferior cava vein compression and poor vascular return.
Plasma volume adjustment	Increasing the plasma volume to 50% to calculate the physiological changes associated with pregnancy in the early second semester.
Hypocalcemia prevention	Calcium gluconate (starting dose 1 g) should be considered to lessen the toxicity of Calcium citrate.
Fibrinogen levels	Consider that the lower baseline of normal fibrinogen will be 50% higher than the baseline of unpregnant individuals to calculate the physiological changes.
Obstetric consultation	Obstetric involvement can help thorough management for both patient and fetus.
Rh status determination and RhIg administration	Plasma exchange can decrease the RhIg levels below the recommended volume. Re-administration of RhIg should be considered following plasma exchange.

left lateral decubitus. The patient has a double lumen installed with a replacement fluid requirement of 2580 mL. For fluid replacement, 5% albumin and citrate dextrose (ACD) anticoagulant are used as anticoagulants. Three calcium supplement tablets were given before each procedure as prophylaxis for citrate poisoning and hypocalcemia. Fibrinogen levels before and during the procedure were within normal limits. During the action, monitoring of the mother's blood pressure and fetal heart rate was carried out by the obstetrics department.

CONCLUSION

Myasthenia gravis crises rarely occur with pregnancy. However, pregnancy can affect the course of myasthenia gravis and can trigger a myasthenic crisis. Prompt diagnosis and appropriate management can reduce the morbidity of MC, especially during a crisis. Therapeutic plasma exchange is a safe and effective procedure for the management of MG during pregnancy, especially for those experiencing myasthenic crisis.

REFERENCES

1. Roper J, Fleming ME, Long B, Koyfman A. Myasthenia gravis and crisis: Evaluation and management in the emergency department. J Emerg Med, 2017; 53(6): 843-853.
2. Shimizu Y, Kitagawa K. Management of myasthenia gravis in pregnancy. J Clin Exp Immunol, 2016; 7: 199-204.
3. Ducci RD, Lorenzoni PJ, Kay CSK, Werneck LC, Scola RH. Clinical follow-up of pregnancy in myasthenia gravis. Neuromuscul Disord, 2017; 27(4): 352-357.
4. Schroeter M, Thayssen G, Kaiser J. Myasthenia gravis–exarcebation and crisis. Neurology International Open, 2018; 2: E10-E15.
5. French DM, Bridges EP, Hoskins MC, Andrews CM, Nelson CH. Myasthenic crisis in pregnancy. Clin Pract Cases Emerg Med, 2017; 1(4): 291-294.
6. Drachman DB, Amato AA. Myasthenia gravis and other disease of the neuromuscular junction. In: Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. Harrison's Principle of Internal Medicine. Nineteenth Ed., New York, McGraw Hill, 2015; 2701-2706.
7. Jovandaric MZ, Milenkovic SJ. Maternal and neonatal outcome of pregnancies with autoimmune myasthenia gravis. In: Al-Zwaini IJ, AL-Mayahi A. Selected topics in myasthenia gravis. London, IntechOpen, 2019; 1-9.
8. Banner H, Niles KM, Ryu M, Sermer M, Bril V, Murphy KE. Myasthenia gravis in pregnancy: Systematic review and case series. Obstet Med, 2022; 15(2): 108-117.
9. Edmundson C, Salajegheh MK. Myasthenia gravis and pregnancy. In: O'Neal, MAO. Neurology and psychiatry of women. Switzerland, Springer, 2019; 177-182.
10. Waters J. Management of myasthenia gravis in pregnancy. Neurol Clin, 2019; 37: 113-120.
11. Bansal R, Goyal MK, Modi M. Management of myasthenia gravis during pregnancy. Indian J Pharmacol, 2018 Nov-Dec; 50(6): 302-308.
12. Patterson ER, Winters JL. Hemapheresis. In: McPherson RA, Pincus MR, editors. Henry's clinical diagnosis and management by laboratory method. Missouri, Elsevier, 2017; 751-782.
13. Cox JL, Koepsell SA, Shunkwiler SM. Therapeutic plasma exchange and pregnancy: A case report and guidelines for performing plasma exchange in a pregnant patient. J. Clin Apheresis, 2016; 32(3): 191-195.