

Dengue Fever in Myasthenic Crisis

Alif Adlan Mohd Thabit^{1*}, Wan Mohd Rasis Wan Ahmad Kamil¹, Mohd Ramadhan Mohd Din²

¹Department of Medicine, Bentong Hospital, Jalan Tras, 28700 Bentong, Pahang, MALAYSIA

²Department of Medicine, Sultan Haji Ahmad Shah Hospital, Jalan Maran, 28000 Temerloh, Pahang, MALAYSIA

ABSTRACT

Aims: To investigate the possibility of a difference in late response towards intravenous immunoglobulin and its efficacy in myasthenic crisis when given during an acute dengue infection.

Presentation of case: We report a 29-year old lady with myasthenia gravis diagnosed two years prior based on clinical presentation and positive anti-cholinesterase receptor antibody (AChR Ab) titre of > 20.98 nmol/L. Dengue infection was confirmed with positive SD® Dengue NS1 (Non Specific-1) antigen test. Muscle strength graded with the Medical Research Council (MRC) scale as well as hematological tests and arterial blood gases were done with chest X-rays to investigate for a concurrent chest infection. The patient was given IVIg 0.4g/kg/day for five days on the fifth day during the febrile phase of dengue fever after being ventilated in ICU for severe type 2 respiratory failure.

Discussion: The patient showed neurological improvement only after twenty five days post-IVIg administration due to ventilator associated pneumonia and *Stenotrophomonas maltophilia* bacteraemia as post viral complications, as compared to five days during her previous uncomplicated myasthenic crisis. From a muscle power of 4/5 bilaterally of upper and lower limb extremities it had improved to 5/5 bilaterally together with improving hematological blood counts which coincides with the resolution of dengue and bacterial infections.

Conclusion: There may be a difference in late response towards IVIg and its efficacy in myasthenic crisis when given during the acute febrile phase of a dengue infection. A future alternative option of plasma exchange should be looked into detail.

Keywords: Dengue fever, myasthenia gravis, myasthenic crisis, IVIg, intravenous immunoglobulin

1. INTRODUCTION

Dengue fever is a common mosquito borne viral infection in tropical countries like Malaysia. In the year 2011, Nor Azila et al reported a high prevalence of up to 91.6% in a cross-sectional study of dengue IgG seroprevalence among 1000 Malaysian adult population between the ages of 35 and 74 years of age [1]. Dengue fever has several systemic manifestations – which include neuromuscular involvements such as myositis [2], Guillain-Barre syndrome [3] and worsening muscle weakness among patients with pre-existing myasthenia gravis (MG). Until today, the pathogenesis of neuromuscular complications as well as the role of host and virus are not clear. Hardjo et al had reported that dengue infection potentially can worsen muscle weakness ie ptosis, cranial nerves palsy and extremity motor strength among MG patients, and improves as the infection resolves [4]. To our knowledge, this is the first reported case of dengue fever presenting with myasthenic crisis. Intravenous immunoglobulin, being one of the treatments for myasthenic crisis was administered to the patient. We propose that there is a difference in clinical

E-mail address: alif.adlan@gmail.com

response of IVIg in this MG patient between her first presentation when first diagnosed as MG and her current presentation with dengue infection.

2. PRESENTATION OF CASE

We report a case of a 29 year-old female diagnosed with myasthenia gravis confirmed two years prior to her current admission. At the time, she presented with two days history of worsening lethargy and fever associated with cough and sore throat. Her condition deteriorated during ward admission and was intubated in view of severe respiratory distress. After 48 hours she was extubated but had to be reintubated again as she had desaturated due to severe aspiration from oral secretions. On further history, she had a preceding history of worsening dysphagia associated with lethargy. Clinical examination revealed no diplopia or ptosis and fatiguability sign was negative. There was presence of proximal myopathy on both upper and lower limbs. Sensation and reflexes were intact.

As the clinical history was suggestive of myasthenic crisis, she was started on an escalating dose of oral pyridostigmine 30mg bd along with intravenous immunoglobulin (IVIg) 0.4g/kg daily for a total of five days and intravenous hydrocortisone 50mg tds. Improvement was observed by the time she had received the total dose of planned IVIg, as she was able to be extubated and self ambulate during her period of recovery. She was discharged with a tapering dose of oral prednisolone and oral pyridostigmine with a planned follow up to be reviewed by neurologists at a tertiary centre. The diagnosis of MG was supported with a positive anti-cholinesterase receptor antibody (AChR Ab) titre of > 20.98 nmol/L. Computed Tomography (CT) Thorax showed no evidence of thymoma.

However, she defaulted follow-up and remained in remission. Her last follow up at the medical clinic less than a year later noted that she was still experiencing fatiguability with occasional ptosis and dysphonia. The dose of pyridostigmine was increased to 60mg qid with concurrent prednisolone therapy. Azathioprine was introduced as a steroid sparing agent during this visit.

During her current presentation, she presented with a 4 days history of fever and acute onset of breathlessness and was diagnosed as having dengue fever based on SD® Dengue NS1 (Non Specific-1) antigen test with no warning signs. Clinically on presentation there were no reported ptosis of the eyes, and the power of the upper and lower limbs were graded 4/5 generally. However in view of the patient's background of MG, she was diagnosed as myasthenic crisis as evidenced by severe type 2 respiratory failure and generalized muscle weakness which required intubation and ventilatory support at the intensive care unit (ICU) at the nearest tertiary medical centre. At the time, her chest X-ray findings were normal with no consolidation changes.

On day 5 of fever, she was given a course of intravenous immunoglobulin 0.4g/kg daily for five days for the crisis. The response to IVIg was determined by the clinical assessment of muscle strength according to the Medical Research Council (MRC) scale, partial pressure arterial carbon dioxide (PaCO₂), and oxygen (PaO₂) in response to controlled fraction of inspired oxygen (FiO₂) ventilator settings (Table 1). However the response was poor and delayed as compared to her first myasthenic crisis. Six days after IVIg, the muscle strength remained similar. However, during the admission, the ventilation was prolonged and the type 2 respiratory failure persisted as she had suffered a ventilator-associated pneumonia associated with *Stenotrophomonas maltophilia* bacteraemia. It was successfully treated with intravenous antibiotics. Upon discharge after 31 days of admission, the muscle strength had normalized but the patient had to be kept on tracheostomy due to the prolonged intubation. At the time of writing three months later, patient was seen to be coping well with her daily life after having the tracheostomy tube removed.

Table 1. Physical examinations and laboratory results of the patient

E-mail address: alif.adlan@gmail.com

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	Day 4 illness	Day 5 illness	Day 8 illness	Day 11 illness	Day 31 illness
Ptosis	Nil				
Extremity motor strength	4/5 upper limbs 4/5 lower limbs			3/5 upper limbs 4/5 lower limbs	5/5 upper limbs 5/5 lower limbs
Haemoglobin (13-18 g/dL)	14.9	14.8	13.8	14	14.1
Haematocrit (36%-47%)	44.5	44.5	43.3	44	44.1
Leucocyte (4-11 $\times 10^9/L$)	3.0	3.0	8	18	12
Platelets (150-400 $\times 10^9/L$)	114	111	90	100	202
PaO ₂ (75-100mmHg)	50.4 (NP 3L/min)	150 (FiO ₂ 50%)		84 (FiO ₂ 40%)	95
PaCO ₂ (35-45mmHg)	51	30		51	32

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83 3. DISCUSSION

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85 **Myasthenic crisis**, characterised by additional respiratory difficulties or distress, can be brought on by the
86 same factors as those that can cause worsening MG symptoms namely systemic diseases (primarily viral
87 respiratory infection), fever and medications affecting neuromuscular transmission.

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89 The pathogenesis of neuromuscular complications of dengue fever are generally categorized into the
90 neurotropic nature of the DENV itself [4], the systemic complications of dengue infection and post
91 infection complications. These may be due to the neurotropic nature of the virus, the systemic infection
92 and even immune mediated [2].

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94 No myalgia symptoms such as muscle aches to suggest of myositis were present in this patient. It is
95 possible that the neurotropic effect of the virus had caused the progressive worsening of the weakness in
96 the early part of the incubation period which eventually lead to the respiratory failure found in **myasthenic**
97 **crisis** during the febrile phase of the dengue infection. As the patient was entering recovery phase of the
98 dengue infection, she remained dependent on ventilatory support as she had developed a ventilator
99 associated pneumonia with *Stenotrophomonas maltophilia* bacteraemia, as a post viral infection
100 complication. This further delayed the process of extubation and the patient's recovery.

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102 Our patient experienced progressively worsening proximal muscle weakness and difficulty in swallowing
103 solids and fluids with respiratory distress requiring intubation two years ago, and diagnosed as
104 **myasthenic crisis**. Her condition improved with IVIg and with oral **pyridostigmine** therapy 60mg qid with

E-mail address: alif.adlan@gmail.com

concurrent oral prednisolone.

However, she was lost to follow up and her symptoms recurred again when she was diagnosed with dengue fever. Her symptoms 2 years ago were similar to her current presentation, with an acute onset of breathless following four days of fever, preceded by progressively worsening generalized weakness of two weeks duration. With an incubation period of four to seven days (range between three to fourteen days), this would coincide with the early part of incubation period. Apart from viraemia, non-compliance to her medications further contributed to the rapid worsening of her MG symptoms.

The benefit of IVIg usually begins within two weeks and lasts several months but only approximately 65% of MG patients are responsive to it [5]. During the patient's first presentation, she had good clinical improvement by the fifth day of IVIg administration, but did not exhibit the same rate of progress when she had the dengue infection. It is not known whether the neurotropic effect of the DENV may have played a role in our patient's delayed response to IVIg, as IVIg acts by diminishing the disease activity for for unknown reasons [6]. On the other hand, plasmapheresis which removes circulating antibodies including those responsible for the disease, has a faster onset of clinical improvement of several days [7]. In the context of this patient, the progress for improvement was complicated even further by a post dengue infection. Zinman L et al reported no difference between plasma exchange and IVIg in a randomized clinical trial. [8]. Whether the use of plasma exchange would lead to a better outcome response thus preventing a post dengue bacterial infection will require more studies in the future.

4. CONCLUSION

We postulate that there may be a difference in late response towards IVIg and its efficacy in myasthenic crisis when given during the acute febrile phase especially with concurrent dengue infection. An option of plasma exchange should be looked into detail with further studies comparing both IVIg and plasma exchange to determine any difference between their efficacy and outcomes.

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6. COMPETING INTERESTS

Authors have declared that no competing interests exist.

7. AUTHORS' CONTRIBUTIONS

'Author A' wrote the first draft of the manuscript. 'Author B' managed the literature searches and all authors read and approved the final manuscript.

8. CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

9. ETHICAL APPROVAL

Not applicable

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E-mail address: alif.adlan@gmail.com

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