

Case study

Dengue Fever in Myasthenic Crisis

ABSTRACT

Dengue fever is a common mosquito borne viral infection in tropical countries like Malaysia, and is associated with neuromuscular involvements such as myositis, Guillain-Barre syndrome and worsening muscle weakness among patients with pre-existing Myasthenia Gravis (MG). The pathogenesis of neuromuscular complications as well as the role of host and virus are not clear, and might be associated with the virus' neurotropic effect, systemic infection effect or simply immune-mediated. We report a case of a 25 year-old female MG patient on cholinesterase inhibitor treatment who presented with four days history of fever and an acute onset of breathlessness. She was diagnosed with dengue complicated with respiratory distress due to myasthenia crises which required intubation and was given a course of intravenous immunoglobulin (IVIg). However, the admission was complicated with a ventilator associated pneumonia due to a prolonged period of intubation. We postulate that there may be a delay in response towards IVIg in myasthenic crises when given during the acute febrile phase of ongoing dengue infection. Hence, more studies are needed to determine whether the timing of administration of IVIg would give better benefit in patients with dengue and concurrent myasthenic crisis.

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. The prevalence of MG has not been well known until 30 years ago, when the earliest available data of MG was from a study which reported a total of 62 cases seen from 1968 to 1979 at the Kuala Lumpur General Hospital, giving an average of 5.16 new cases every year [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) [4]. The pathogenesis of neuromuscular complications as well as the role of host and virus are not clear, and might be associated with the virus' neurotropic effect, systemic infection effect or simply immune-mediated. To our knowledge, this is the first reported case of dengue fever presenting with myasthenia crisis treated with immunotherapy ie immunoglobulin.

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. In view of this new event and further history probed that she had had preceding history of worsening dysphagia associated with lethargy. Clinical examinations revealed no diplopia or ptosis and fatiguability sign negative. There was presence of proximal myopathy both upper and lower limbs. Sensation and reflexes were intact.

As the clinical history was suggestive of a myasthenic crises, she was started on 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. The progress was seen by the time she had received the total dose IVIg planned, as she was able to be extubated and self ambulate. She was discharged with a tapering dose of oral prednisolone and oral Pyridostigmine with a planned follow up with neurologists at a tertiary centre. The diagnosis of MG was supported with a positive anti-cholinesterase receptor antibody (AChR Ab) 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 to us at Bentong Hospital, a district hospital, she presented with a 4 days history of fever and acute onset of breathlessness and was diagnosed having Dengue Fever (NS Antigen positive) 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 patient's background of MG, she suffered myasthenia crises evident by severe Type 2 respiratory failure and generalized muscle weakness which required intubation and ventilator support at the intensive care unit (ICU) at a tertiary medical centre, Temerloh Hospital.

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 had to still be 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

	Day 4 illness	Day 5 illness	Day 8 illness	Day 11 illness	Day 31 illness
Ptosis	Nil				
Extremity	4/5 upper limbs			3/5 upper limbs	5/5 upper limbs
motor	4/5 lower limbs			4/5 lower limbs	5/5 lower limbs
strength					
Haemoglobin	14.9	14.8	13.8	14	14.1
(13-18 g/dL)					
Haematocrit	44.5	44.5	43.3	44	44.1

(36%-47%)					
Leucocyte	3.0	3.0	8	18	12
(4-11 x 10 ⁹ /L)					
Platelets	114	111	90	100	202
(150-400 x 10 ⁹ /L)					
PaO ₂	50.4	150		84	95
(75-100mmHg)	(NP 3L/min)	(FiO ₂ 50%)		(FiO ₂ 40%)	
PaCO ₂	51	30		51	32
(35-45mmHg)					

3. DISCUSSION

Being an autoimmune disease, MG affects the neuromuscular junction at the post synaptic membrane nicotinic receptors, where it is affected by antibodies which reduces its effectiveness. The hallmark of MG being muscle weakness brought on by prolonged muscle use which is described as fatiguability - progressive on exertion and relieved at rest. Myasthenic crises, characterised by additional respiratory difficulties or distress, can be brought on by the same factors as those that can cause worsening MG symptoms namely systemic diseases (primarily virus respiratory infection), fever and medications affecting neuromuscular transmission.

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

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

Our patient experienced progressively worsening proximal muscle weakness and difficulty in swallowing solids and fluids with respiratory distress requiring intubation two years ago, and diagnosed as myasthenia gravis in crisis. Her condition improved by intravenous immunoglobulin and with oral pyridostigmine therapy 60mg four times daily with 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. It was then confirmed on presentation that the patient had dengue fever based on NS1 (non-specific 1) antigen positivity. 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]. 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. Whether the timing for an earlier administration of IVIg 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 delay in response towards immunoglobulin in myasthenic crises when given during the acute febrile phase of ongoing dengue infection. As a result, post dengue bacterial infection may further prolong the recovery period in an intubated patient. Hence, more studies are needed to determine the response of MG patients in myasthenic crisis with concurrent dengue infection in its course towards intravenous immunoglobulin.

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

10. REFERENCES

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148
149
150
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