

## Review

# Neuromyelitis Optica: Hospital Universiti Sains Malaysia Experience

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### Abstract

To report clinical presentation and outcome of Neuromyelitis Optica (NMO) in Hospital Universiti Sains Malaysia. An observational, retrospective case series of patients with NMO attended Hospital Universiti Sains Malaysia from July 2006 to June 2010. All patients were co-managed by neurologist and neuro-ophthalmologist and attended neurology and ophthalmology clinic. All four patients were Malay. There were two males and two females. The age ranged from 26 to 40 years. The mean age of onset was 27.5 years for the monophasic group, and 34 years for the relapsing group. Both females had the relapsing type. Three out of four patients had unilateral optic neuritis as their initial presenting event, with only one patient presented as acute myelitis. The diagnosis of NMO was made based on the revised criteria proposed by Wingerchuk. All patients were treated with intravenous methylprednisolone during the acute attack. Only 1 patient was started on systemic Azathioprine. One patient with the monophasic type has good visual recovery, whereas the other patient was defaulted follow up. Both patients in the relapsing group had poor visual outcome due to optic atrophy. The clinical presentations of our patients are parallel with other published series. All the patients are young adults, and the monophasic group has an earlier onset compared to the relapsing group. The relapsing group had poor visual outcome due to optic atrophy.

**Keywords:** Neuromyelitis Optica, NMO, Devic's disease.

## INTRODUCTION

Neuromyelitis Optica (NMO) is also known as Devic's disease. It is an inflammatory disease with predilection for optic nerves and spinal cord, which can occur simultaneously, or separated by variable period of time. NMO has been classified as a subtype of multiple sclerosis (optic spinal recurrence form of multiple sclerosis) but there are increasing evidences that it is a uniquely distinct entity altogether. It has been reported that in Asia and India, the demyelinating disease is often limited to the optic nerve and spinal cord.

The recent NMO literature indicates NMO can be either a fulminating monophasic disease (20%) or more typically one that is polyphasic (80%), characterized by relapses and remissions with variable degrees of

recovery between episodes (Wingerchuk et al., 1999). Patients with NMO present with acute, often have severe attacks of blindness and paraparesis or quadriparesis, accompanied by sensory and sphincter impairments. All NMO patients satisfied criteria of Wingerchuk et al., 2006 which include two major symptoms, optic neuritis and acute transverse myelitis. In 2006, revised criteria for NMO were proposed. Beside the above criteria, any two of the following three criteria: extended myelitis on spinal cord Magnetic Resonance Imaging (MRI), normal brain MRI at onset and NMO-IgG seropositive status are needed to diagnose NMO (Wingerchuk et al., 2006).

In 2004, a specific pathogenic antibody called NMO-IgG was discovered in 50–70% of patients (Lennon et al., 2004). This antibody is targeted against the aquaporin-4 (AQP4) water channel widely expressed in the optic nerves, the spinal cord and the periventricular regions (Pittock et al., 2006; Lennon et al., 2005). The detection of anti-AQP4 antibodies/ NMO –IgG has been

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Administration of high-dose IV methyl-prednisolone (1 g daily for 3–6 days) is typically the first treatment given to patients with NMO to reduce disease activity and further progression and restore neurologic function. However, in some cases this first-line treatment is not sufficient to reduce the inflammatory process. Another choice is to do plasma exchange. Plasma exchange improves clinical outcomes for steroid-unresponsive relapses (Graber et al., 2008). Intravenous immune globulin is sometime tried for acute NMO attack but data is limited.

### Case 1

A 29 year-old Malay man, a previous intravenous drug user, presented with sudden blurring of left eye vision for 3 days duration. It was associated with pain on eye movement. There were no systemic symptoms. On examination, he was only able to count finger in his left eye while the right eye was 6/6. There was relative afferent pupillary defect (RAPD) in the left eye. Anterior segment examination was unremarkable. Fundoscopy showed hyperaemia and swollen of the left optic disc. The right disc was pink with distinct margin. His anti Hepatitis C Virus (HCV) antibody test was positive, otherwise other blood investigations including full blood count, erythrocyte sediment rate (ESR), venereal disease research laboratory (VDRL), Human Immunodeficiency Virus (HIV) screening, and Mantoux test were normal. MRI revealed hyperintense and swelling of the left optic nerve. The brain was normal. A diagnosis of idiopathic left optic neuritis was made. He was treated with intravenous methylprednisolone 250mg QID for 3 days, followed by oral prednisolone 1mg/kg/day for 11 days and was tapered down over 1 month. His vision improved to 6/9 in 2 weeks and 6/6 in 2 months. He was well until six years later when he presented with similar problem of having sudden blurring of vision in the left eye. There was no systemic symptom of note. On examination left visual acuity was non light perception with marked RAPD. The right eye vision was 6/6. Fundoscopy showed hyperaemic and swollen of the left optic disc. The right optic disc was normal. Repeat MRI showed similar finding of swollen left optic nerve (Figure 1). Additional blood investigations including screening for autoimmune disease and collagen vascular disease were done which were normal. He was diagnosed to have recurrent idiopathic left optic neuritis and was given the same regime of corticosteroid. His vision improved to 6/12 in 2 weeks. Six months after the second attack, he presented with body weakness associated with urinary incontinence. There was no

ocular symptom. MRI brain was normal. However, there were multiple intramedullary abnormal hyperintense lesions seen extending from C1 to C6 and T3 to T4 level. A diagnosis of NMO was made. His body weakness resolved without deficit but urinary incontinence persisted.

### Case 2

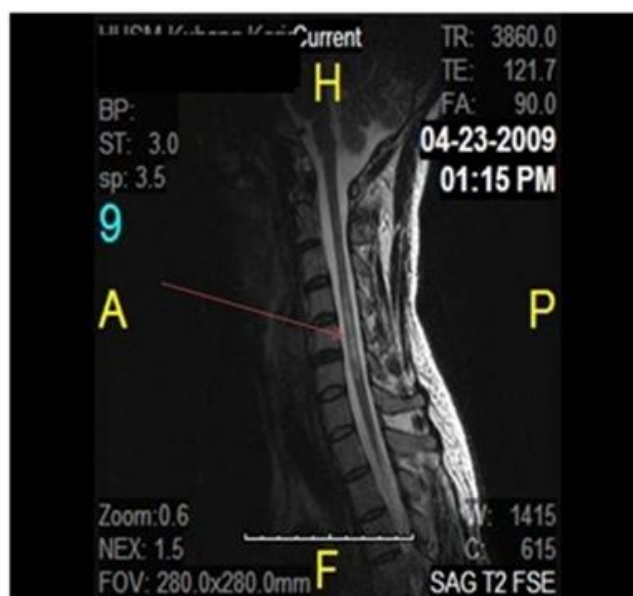
A 26 year-old Malay man who was previously well presented with sudden painless blurring of left eye vision of 1 week duration. There were no associated systemic symptoms. On examination left vision was counting finger with presence of RAPD. Fellow eye vision was 6/6. Anterior segment examination was unremarkable. Fundoscopy revealed left optic nerve swelling and hyperaemia. The right optic disc was normal. Blood investigation including full blood count, ESR, connective tissue screening, VDRL were within normal limit. Mantoux test and chest radiography were unremarkable. MRI showed hyperintense and swelling of the left optic nerve. The brain was normal. A diagnosis of idiopathic optic neuritis was made. He was treated with intravenous methylprednisolone 250mg QID for 3 days, followed by oral prednisolone 1mg/kg/day for 11 days. His left vision improved to 6/12 with pin hole of 6/9 on completion of corticosteroid treatment. However, he was readmitted within 3 weeks after discharged for bilateral sudden painless blurring of vision for 1 week. It was associated with upper and lower limb numbness and incomplete voiding. On examination, his right eye vision was non light perception, and left eye was 6/18 with pin hole of 6/9. Anterior segment was unremarkable. Fundoscopy revealed swollen and hyperaemic right optic disc whereas the left disc was normal. MRI brain was normal. Multiple hyperintense intramedullary lesions were seen in cervical (Figure 2), thoracic and thoracic level on T2 signal. He was started on intravenous methylprednisolone 1g daily for 5 days, followed by oral prednisolone 1mg/kg/day which were tapered down slowly within 1 month. His right vision improved to counting finger and 6/7.5 in the left eye 2 weeks after treatment. His motor symptoms however persisted. Patient was defaulted follow up subsequently.

### Case 3

A 37 year-old Malay lady with history of recurrent idiopathic bilateral optic neuritis presented with sudden loss of left vision and pain on eye movement of one day duration. Five days earlier, she had bilateral lower limb paresis, back pain and difficulty in urination. There were no other systemic symptoms. On examination, left vision was perception of light and fellow eye was 6/9. There was relative RAPD in the left eye. Anterior segment examination of both eyes was normal. Fundoscopy



**Figure 1.** Left optic nerve enlarged and thickened in keeping of optic neuritis



**Figure 2.** Multiple elongated intramedullary abnormal signal intensity of the spinal cord extending from the level of C1 to C2

showed bilateral pale optic disc in both eyes. Blood investigation including full blood count, ESR, connective tissue screening, VDRL were within normal limit. Mantoux test and chest radiography were unremarkable. MRI revealed hyperintense and swelling of the left optic nerve. The brain was normal. There were multiple hyperintense lesions at the level of C4 to C7, and T4 to T10 of spinal cord in T2 signal MRI (Figure 3). A diagnosis of neuromyelitis optica was made and he was started on intravenous methylprednisolone 1g daily for 5

days, followed by oral prednisolone 1mg/kg/day for 4 months, and oral Azathioprine 50mg daily. Her visual acuity improved to count finger close 2 weeks after presentation. On follow up at 6 month her left vision improved to 1/60. Unfortunately, 4 months later, she complained of sudden decreased of vision in the right eye with pain on eye movement. On examination, right vision was non light perception. RAPD was equivocal. Both optic discs appeared pale. She was started on intravenous methylprednisolone 250mg QID for 3 days,



**Figure 3.** Area of abnormal intensity changes seen involving spinal cord of thoracolumbar spine

followed by oral prednisolone 1mg/kg/day for 11 days. Oral corticosteroid was tapered down over 1 month. Oral Azathioprine 50mg daily was added. VEP showed delayed of signal in both eyes. Her right vision improved slightly to hand movement at 2 weeks and counting finger at 3 months. The visual acuity remained counting finger in both eyes during final follow up due to bilateral optic atrophy.

#### Case 4

A 49 year-old Malay lady presented with first episode of sudden painless loss of vision in the right eye of 3 days duration. Nine years ago, she was diagnosed with transverse myelitis which left her paraplegic from waist downwards and unable to control micturition. There were no systemic symptoms. On examination, she was not able to perceive light in the right eye, and left vision was 6/6. There was right RAPD, other anterior segment findings were unremarkable. Fundoscopy revealed pale right optic disc. The left optic disc was pink with well defined margin. Blood investigation including full blood count, ESR, connective tissue screening, VDRL were within normal limit. Mantoux test and chest radiography were unremarkable. MRI brain showed generalised cerebral atrophy. She was diagnosed to have NMO. Patient was started on intravenous methylprednisolone 1g daily for 5 days, followed by oral prednisolone 1mg/kg/day for 11 days. Her right vision improved to count finger after 2 weeks. However she was defaulted follow up until 2 months later when she presented with bilateral sudden blurring of vision of 2 day duration.

There were no other systemic symptoms. On examination, her right vision was non light perception and 6/18 same with pin hole in the left eye. Fundoscopy showed pale disc in the right eye. The left optic disc appeared swollen and hyperaemic (Figure 4). Similar corticosteroid regime was started. Her left vision improved to 6/9 in 2 weeks time, with the right eye improved slightly to hand movement. Unfortunately, in the subsequent five years, she had almost yearly recurrent attacks of left retrobulbar neuritis. Her left vision was deteriorated since then from 6/18 to 6/60. The vision remained hand movement in the right eye. Both eyes had optic atrophy.

#### DISCUSSION

Numerous classifications have been proposed for the diagnosis of Neuromyelitis Optica (NMO). In 2006, Wingerchuck and associates revised their previous criteria in 1999. They proposed the definite diagnosis of NMO must include optic neuritis, acute myelitis and at least two out of three supportive criteria: 1) contiguous spinal cord MRI lesion extending over  $\geq 3$  vertebral segments; 2) brain MRI not meeting diagnostic criteria for multiple sclerosis; and 3) NMO-IgG seropositive status (Wingerchuck et al., 2006). All our patients fulfilled the above criteria for diagnosis of NMO.

Similar to multiple sclerosis (MS), NMO primarily affects the young adult. The pathological hallmark in MS is demyelinating plaque with the axons relatively preserved, whereas in NMO the axons and myelins are involved (Kira, 2008). In NMO, men are reported to have



**Figure 4.** Left optic nerve appeared swollen and hyperaemic

slight preponderance in the early course, and this ratio reverses as the disease progresses to the relapsing course (Wingerchuk et al., 1999). In our case series, the patient's age ranges from 26 to 40 years. All female had the relapsing type. The mean age of onset is 27.5 years for the monophasic group, and 34 years for relapsing group. This is quite similar to the pattern reported by Wingerchuk et al where the mean age of onset is 29 years for monophasic patients and 39 years for relapsing patients (Wingerchuk et al., 1999). On the other hand, the mean age of diagnosis of NMO in our patients is 30.5 years in the monophasic group, and 43 years in the relapsing group. All our patients are of Malay ethnic.

None of our patients had prodromal syndromes that precede the onset of the disease, which is reported to occur in 30-50% of cases (Wingerchuk et al., 1999). These include headache, fever and myalgia. Three out of four of our patients had unilateral optic neuritis as their initial presenting event, with only one patient presenting as acute myelitis. In the Mayo clinic series, 52% of patients had either unilateral or bilateral optic neuritis as their initial clinical presentation. In contrary, JF Rivera and co workers in their Mexican case series found that the most frequent initial clinical presentation was concomitant optic neuritis and myelitis (41%) (Rivera et al., 2008). Our patients in case 1 and 3 had recurrent optic neuritis whom subsequently developed myelitis alone or concomitant with optic neuritis. This led us to revise the diagnosis to NMO. De Seze and colleagues reported that about 20% of their patients with relapsing inflammatory optic neuritis (RION) had subsequently converted to NMO, in which 50% of them were seropositive with NMO-IgG (Seze et al., 2008). Recurrent optic neuritis should therefore probably be considered as a risk factor for developing future NMO.

The relapsing type has always been known to carry

a worse prognosis as compared to the monophasic type. Wingerchuk in his Mayo clinic series analyzed the visual acuity at the last available assessment of 43 patients with relapsing disease and reported 60% of patients had complete blindness (acuity less than 20/200) in at least one eye (Wingerchuk et al., 1999). In our case series, patients with the relapsing type (case 3 and 4) did not do well with visual outcome of at least counting finger or poorer. On the other hand, patient in case 1 with monophasic type had good visual recovery. Patient in case 2 whom we included in the monophasic group, defaulted follow up after 2 weeks of diagnosis of NMO. This probably explained the poor visual outcome in the right eye as the last visual acuity was taken immediately 2 weeks after the episode of optic neuritis and there was no sufficient time for the optic nerve to recover.

Several diagnostic tests are helpful to support the diagnosis of NMO. A normal MRI brain, presence of spinal cord lesion that extends over three or more vertebral segments of the cord and together with seropositivity of NMO-IgG status can help to discriminate NMO from typical multiple sclerosis (Wingerchuk et al., 1999; O'Riordan et al., 1996). Detection rate of NMO-IgG was reported to range from 56.8% to 73% in a few NMO case series (Jun-ichi Kira, 2008). Wingerchuk et al has excluded cerebrospinal fluid (CSF) findings (CSF pleocytosis ( $>50$  WBC/mm<sup>3</sup>) OR  $> 5$  neutrophils/mm<sup>3</sup>) as one of the major supportive criteria in their revised NMO diagnostic criteria. Recently, much has been debated regarding the role of antibodies to aquaporin-4 (AQP4) in pathogenesis of NMO. The detection rate ranges from 35% to 91% in three Japanese series in patients with NMO and optic spinal multiple sclerosis (OSMS). Jun-ichi Kira et al recommended testing for anti-AQP4 antibody for those with longitudinally extensive myelitis, relapsing myelitis, severe or bilateral optic neuritis, relapsing optic neuritis, OSMS, clinically

**Table 1.** Clinical Features

Clinical Features	Monophasic	Relapsing	Total
N	2	2	4
F/M (% F)	0/2 (0)	2/0 (50)	2/2 (50)
Mean age at onset	27.5	34	30.8
Mean age at diagnosis	30.5	43	36.8
Initial event (%)			
Unilateral ON	2 (100)	1 (50)	3 (75)
Bilateral ON	0 (0)	0 (0)	0 (0)
Transverse myelitis	0 (0)	1 (50)	1 (25)
Other myelitis	0 (0)	0 (0)	0 (0)

**Table 2.** Visual acuity and clinical course

Patient (No)	Gender	Initial Event	Clinical Type	Number of Relapses	Worst VA (OD; OS)	Final VA (OD; OS)
1	M	ON	M	0	NPL; 6/18 ph 6/9	CF; 6/7.5
2	F	ON	R	1	1/60; NPL	CF; CF
3	M	ON	M	0	NPL; 6/6	6/12; 6/6
4	F	TM	R	7	NPL; 6/18	HM; CF

isolated syndrome or MS with autoantibodies, and those with extensive white matter lesions. Unfortunately, we do not have the facility to test for either antibodies to AQP4 or NMO-IgG at our centre, and the diagnosis of NMO was made based on clinical and MRI findings. Currently there is no cure for NMO, nonetheless symptomatic treatment can be offered to most patients. Some patients did recover, but many are left with variable degree of visual impairment and spinal dysfunction. The mainstay of therapy is treatment of acute attacks, prevention of medical complications, and rehabilitation. All of our patients were treated with intravenous methylprednisolone (1g/day for 3 to 5 days) during acute attack. For those unresponsive to methylprednisolone, plasmapheresis can be used as second line therapy, with the rationale of removing circulating immune complexes or AQP4 antibodies (Graber et al., 2008). Maintenance immunosuppressive therapy e.g. Azathioprine (2.5 mg/kg/day) or methotrexate is also helpful to prevent disability resulting from further relapses (Jun-ichi Kira, 2008). Only 1 patient in our series was started on Azathioprine. Other treatment modality includes biological agent Rituximab, which appears to reduce the frequency of attacks with subsequent stabilisation or improvement in disability (Jacob et al., 2008).

## CONCLUSION

The characteristic of our patients do not differ much from those presented in other series. Our patients are young,

and the monophasic group has an earlier onset compared to the relapsing group. The latter group tends to perform worse in their course of disease. We were not able to perform the NMO-IgG and anti AQP4 test on our patients, but we plan to recall them for this purpose. To the best of our knowledge, this is so far the first NMO case series in Malaysia to be reported in the literature.

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