

Devic's syndrome: a case report

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Abstract

Objective: to report a case of Devic's syndrome, emphasizing its diagnosis, in addition to reviewing the medical literature.

Description: A female, fourteen-year-old patient suddenly developed weakness in right sided upper limb, numbness in the left lower limb and also diplopia with resolution during hospital stay. However, as the weakness disappeared, blur of vision occurred. The symptoms disappeared after the use of prednisone.

Comments: The diagnostic and therapeutic approach was similar to that used in other cases reported by different reference centers. However, prednisolone and other immunosuppressant therapy were used for relapsing symptoms. Besides, there is still some controversy surrounding its etiology and relationship with other demyelinating diseases, such as multiple sclerosis.

Case report

In July 93 a Thai fourteen-year-old female child was admitted to the emergency room of the Ramathibodi's Hospital with suspicion of Multiple sclerosis.

Two months before she had presented with horizontal diplopia, diffuse headache and dorsal neck pain. The result of an eye examination at Chumpon's Hospital was normal.

One week previous to admission, she developed walking and writing difficulty in her right body side and generalized numbness especially in the left lower limb. Positive pertinent findings on neurological examination are as following:

Full EOM, normal fundoscopic examination, 3 mm pupillary size which normally react to light in both eyes, no facial palsy, normal gag reflex, positive right sided clonus test, presentation of Babinski's sign in both sides, grade III muscle power of right upper limb, grade V muscle power of all other parts, decreased pin prick sensation of both hands, impaired joint position sense at right side, 3+ deep tendon reflex on the right and 2+ on the left side and positive *Lhermitte's* sign.

The results of lab exams: The CSF showed WBC 16 cell/Cumm (PMN 13%, Lymphocyte 87%), RBC 15 cell/Cumm, sugar 45 mg/dl, protein 57 mg/dl which slight increase in the amount of % gamma globulin of total protein 10%, normal VEPs, normal finding in brain CT scan. First multiple sclerosis with no characteristic lab exam but typical clinical presentation was suspected. Serologic work up as ANA is positive 1:320. Therapeutic plan during the hospital stay: use of prednisone 40 mg/day for two days; after that, the dose will be reduced to 30 mg/day.

Outpatient followup: Unfortunately after the use of corticosteroids for one month the patient developed paraesthesias on both upper limbs. Since then she was diagnosed with multiple sclerosis with corticosteroid dependence. Afterwards the neurologist adjusted the dose of corticosteroid by the patient's clinical presentation for three years. Finally, she could taper off corticosteroid for eight years without any relapse of the disease.

In July 06, when the patient was 25 years old, the paraesthesia symptoms occurred again, including the patient's affected eyesight. She had blurred vision on right eye. On ophthalmologic exam positive RAPD on right eye was revealed. Consultation for further eye examination was done. The ophthalmologist impressed relapsed multiple sclerosis with retrobulbar optic neuritis, especially at the right eye. Another investigation at that time was a MRI of the whole spine. A non-enhancing MS plaque extending from C1-C5 level with possible early cord

atrophy was found. Because she wanted to be treated at her hometown in south of Thailand, she received methylprednisolone 1 g IV injection once daily for three days and after that oral prednisolone (5 mg) 4 tablets three times a day according to a neurologist of Ramamthibodi's suggestion.

In July 09, the patient was admitted to Ramathibodi's hospital with a presentation of acute progressive right hemiparesis with suspended sensory loss. According to the previous history of retrobulbar optic neuritis, the clinical examination was compatible with Devic's syndrome (Neuromyelitis optica) for which a loading dose of methylprednisone 1g was administered via IV once daily for three days. The patient's home medication was prednisolone (5 mg) 4 tablets, three times a day for 1 week, dropping down the dosage on the following day to 1 tablet a week for the further 5 weeks. Additionally she got Azathioprine, an immunosuppressant with dosage adjustment by the neurologist on every follow up. Besides, the patient was reviewed by physiotherapists and the Rehabilitation Service where she had been hospitalized as usual. Due to improving her symptoms prednisolone was drawn 2 months later.

In September 09, she presented with tonic spasm of her right hand. She said not to be able to write a letter. From that time on she was treated with carbamazepine. Fortunately the patient didn't have relapsed multiple sclerosis so far.

In June 11, the now thirty year old patient developed tingling and numbness of her right upper limb. Neurological exam showed no significant abnormality except positive RAPD and optic disc atrophy at the right eye. Because of her right neuralgic paraesthesia, the neurologist ordered her nortriptyline (10mg) 1 tablet before bedtime and continued azathioprine (50mg) 1 tablet once daily and carbamazepine (200mg) 1 tablet twice a day. Outpatient follow up: In the CSF exam, the oligoclonal band was negative. Anti-NMO-IgG was positive and VEP revealed prolonged bilateral P100 latencies. She was treated by the same dose of azathioprine and nortriptyline as previous and the neurologist decided not to treat her by carbamazepine any more because of missing tonic spasm.

The last admission at emergency department is on Oct 25th 2011. She presented with weakness on her right leg 1 week and felt numb on both

leg. Neurological examination showed: no direct pupillary light reaction and positive RAPD in the right eye. Visual sensibility on right eye was absent. Pale right optic disc was found on funduscopic exam. All deep tendon reflexes were 3+. The cranial nerves were normal. Muscle power of elbow extensors, finger extensors, hip extensors and hip/knee/ankle flexors were grade IV, the others were grade V. Muscle tone at right sided upper and lower limb were more spastic than left side. Decreased pinprick sensation at C5-C6, T3-S5 on the right side and T3-T11 on the left side. Decreased joint position sensation at left hip joint and metacarpophalangeal joints. Lhermitte's sign was negative. Babinski's sign was presented on the right side. The management plan at that time was the exclusion of any infection first. If the results will show no evidence of infection, the patient would be treated by methylprednisolone 1 gram IV for 5 days and followed by oral prednisolone (5 mg) 4 tablets three times daily for 1 week then 3 tablets three times daily for another 1 week. Other home medications would remain same as before. Next appointment would be in the next 3 weeks.

Discussion

Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system that causes severe optic neuritis and myelitis attacks. It tends to spare the brain early in the disease course.

The traditional concept of NMO was that of a monophasic disorder consisting of bilateral optic neuritis and severe 'transverse' myelitis occurring simultaneously or in rapid succession (within two weeks). Late 20th century definitions were more inclusive and allowed for unilateral optic neuritis, a longer inter-attack interval (months or years), and a relapsing course.¹⁻³ Diagnostic criteria have recently been revised.⁴

Characteristics of NMO that help to distinguish it from classical MS include:

- More severe optic neuritis and myelitis attacks
- Prominent CSF pleocytosis (more than 50 WBC) that can be dominated by polymorphonuclear cells¹⁻³
- Lower frequency of CSF oligoclonal banding (15-30% compared with 85% in MS)¹⁻³
- At disease onset, the brain MRI scan is normal or reveals nonspecific white matter lesions that do not meet MS MRI diagnostic criteria.

- During acute myelitis attacks, spinal cord MRI scans disclose a contiguous, longitudinally extensive lesion, centrally based in the cord and extending over three or more vertebral segments. MS lesions are more peripherally located in the cord and are less than one to two segments in length.

Based on this patient's history, she had negative CSF oligoclonal banding and spinal cord MRI scans disclose a contiguous, longitudinally extensive lesion, centrally based in the cord and extending C1-C5 vertebral segments.

Despite this patient with optic neuritis and myelopathy may fulfill both a diagnosis of MS, and a diagnosis of NMO, according to the criteria of Wingerchuk et al. (Table 1)³. Normal brain MRI at onset is not an exclusion criterion for MS [18,19]. We therefore consider that, in order to definitely exclude MS, the criteria of Wingerchuk et al.³ should be revised as follows. The presence of absolute criteria (Table 1) and at least two of the following four: (1) negative brain MRI at onset; (2) spinal cord MRI with signal abnormality extending over three or more vertebral segments; (3) CSF pleiocytosis of >50 WBC/mm³; (4) residual visual acuity of less than 20/200 in at least one eye. This case meets absolute criteria and also two of those in number 2 and 4. Using these revised criteria, MS patients with negative MRI at onset can be excluded⁴⁻⁵.

Clinical Features of NMO

- Optic neuritis

Optic neuritis attacks in NMO are typically more severe than those in MS. Complete visual loss, pain with eye movement, and incomplete recovery are typical. Bilateral simultaneous optic neuritis is a hallmark of NMO but rare in MS.

- Myelitis

Spinal cord attacks cause rapidly progressive paraparesis or quadriparesis, loss of sensation below the site of inflammation, and bladder and bowel retention or incontinence. Neck or back pain at or just below the lesion and L'hermitte's symptom (spinal or limb paresthesias elicited by neck flexion) are common. Nearly half of the patients also experience repetitive painful spasms of one or more limbs. These 'paroxysmal tonic spasms' last 30-45 seconds and recur dozens of times per day.³ Spinal cord lesions that ascend into the brain stem may cause neurogenic respiratory failure.

The clinical features of Devic's Syndrome (Neuromyelitis optica, Devic's disease) include temporary blindness in one or both eyes, weakness or paralysis, painful spasms, and bladder and bowel problems. In this case, the patient has finally blindness on the right eye, even she developed her diplopia symptom almost 15

years ago. Clinical manifestations of this syndrome are caused by optic neuritis and transverse myelitis. It may follow monophasic or relapsing course as same as in this patient. She also has a progressive paraparesis or quadriparesis, loss of sensation below the site of inflammation, neck or back pain at or just below the lesion and L'hermitte's symptom. Spinal cord lesions that ascend into the brain stem may cause neurogenic respiratory failure but this is not found in this case. Tonic spasm (paroxysmal dystonias, tonic seizures) is characterized by painful unilateral contractions of the upper or lower extremities⁴⁻⁵. This patient also had that tonic spasm in September, 2009. Sometimes the attacks are stimulated by tactile stimulation or movement and are predated by transient sensory disturbance.

- Other symptoms

It is now recognized that neurological symptoms in NMO may occur due to involvement of brain structures outside of the optic nerve or spinal cord.⁴ Extension of a cervical spinal cord lesion may cause, in addition to respiratory failure, hiccups, vomiting, vertigo, diplopia, and ataxia.^{3, 8-9} Diplopia is a symptom at the first presentation of this patient. Cerebral lesions are rarely symptomatic but when present do not exclude the diagnosis of NMO.

Discovery of NMO-IgG

The association of NMO with the serum autoantibody marker NMO-IgG was reported in 2004.⁸ NMO-IgG is 73% sensitive and 91% specific for distinguishing NMO from optic-spinal presentations of classical MS. In 2006, NMO-IgG was integrated into the new NMO diagnostic criteria (Table 1).³ The newly-proposed criteria are 99% sensitive and 90% specific for NMO in patients presenting with optic-spinal disease presentations of CNS demyelinating disease. Although the NMO-IgG blood test is a very useful diagnostic tool, a diagnosis of NMO may be achieved using a new criteria without the NMO-IgG test and in patients whose NMO-IgG test is negative. By the way, the result of NMO-IgG was positive in this patient.

The target antigen of NMO-IgG is aquaporin-4 (AQP4). AQP4 is the most abundant CNS water channel. It facilitates water transport, especially in "stress situations" such as brain injury. It is not known whether NMO-IgG causes NMO or if it is simply a marker of the disease. Further experiments will include attempts to establish an animal model of NMO and determine the pathogenic role of NMO-IgG. Several investigators have reported patients with isolated myelitis (i.e. without optic neuritis) who are NMO-IgG positive and who are now

considered to have NMO spectrum disorders. Increasing evidence points to a high frequency of NMO-IgG seropositivity at an early point of the illness, generally at the first attack, and to the pathogenic role of aquaporin-4 antibodies.

The Clinical Spectrum of NMO

The specificity of NMO-IgG has expanded the clinical spectrum of NMO. It allowed confirmation that brain lesions may occur in NMO, occasionally in a rather specific pattern that includes the hypothalamus and regions adjacent to the third and fourth ventricles.^{4, 13} NMO-IgG seropositivity rates are approximately 50% in patients with recurrent longitudinally extensive transverse myelitis (LETM) and about 25% in patients with simultaneous or recurrent optic neuritis and negative brain MRI.¹¹ Patients presenting with a first-ever LETM event and who are found to be NMO-IgG seropositive have a 56% risk of LETM recurrence or optic neuritis (conversion to NMO) during the subsequent 12 months.¹⁴ These findings suggest that single or recurrent events of LETM, bilateral simultaneous optic neuritis, and recurrent optic neuritis are, at least in some cases, limited or incompletely developed forms of NMO. Furthermore, NMO-IgG appears to be a highly specific marker for Asian optic-spinal MS. In a Japanese cohort, 58% of patients with optic-spinal MS were NMO-IgG seropositive compared with none of the “conventional” or “Western” MS pattern.¹¹

NMO-IgG has informed debate about the relationship of systemic autoimmune disorders (e.g., systemic lupus erythematosus (SLE) or Sjögren’s syndrome (SS)) to transverse myelitis and NMO. Some consider that if clinically evident SLE or SS, or positive autoantibodies associated with those disorders (antinuclear antibody; antibody to extractable nuclear antigen), coexist with NMO symptoms and signs that the neurological process is a vasculitic complication of the systemic disorder. In this case, we found that she had positive ANA with 1:320 titers without further investigations for systemic disorder. However, recent studies¹⁵⁻¹⁶ demonstrated that:

- 1) NMO-IgG does not occur in individuals with clinically-defined SLE or SS who lack symptoms or signs of an NMO spectrum disorder
- 2) NMO-IgG more commonly is detected in patients with NMO symptoms who have clinical or serological evidence for SLE or SS than in those who do not.

Therefore, co-occurrence of NMO with SLE or SS, at least in NMO-IgG seropositive patients, represents the coexistence of two autoimmune diseases rather

than an indication that patients have developed a secondary vasculitic complication of the systemic disorder.

In summary, the high specificity of NMO-IgG has provided an insight into an expanded clinical spectrum of disorders that comprise the NMO spectrum (Table 2).

Diagnostic Approach

NMO should be considered in any patient presenting with simultaneous bilateral optic neuritis or sequential recurrent optic neuritis with a negative brain MRI scan. It should also be considered with presentation of a single event or recurrence of LETM (“transverse myelitis” with a contiguous ≥ 3 segment spinal cord MRI lesion).

All patients should have a cranial MRI scan with intravenous gadolinium administration. Brain imaging will determine the presence and pattern of lesions that assist in diagnosis. At disease onset (first attack), a normal brain MRI, or one that reveals lesions not meeting MS MRI criteria, fulfills one of the three major supportive diagnostic criteria for NMO. If the diagnosis of NMO is being considered months or years after disease onset, it may be necessary to obtain the first MRI, if it exists, to evaluate this criterion. *The presence of brain MRI lesions does not exclude a diagnosis of NMO.* A pattern of T2-weighted abnormality in AQP4-rich areas, such as the hypothalamus or around the third or fourth ventricle, may be specific for NMO. During optic neuritis attacks, an orbital MRI protocol may identify optic nerve gadolinium-enhancement, providing strong evidence toward an inflammatory etiology.

Patients with myelitis should have a cervical and thoracic spinal cord MRI scan with intravenous gadolinium administration to evaluate for the presence of a longitudinally extensive cord lesion, which is the second major supportive diagnostic criterion. The presence of patchy or noncontiguous, short segment lesions in the setting of acute myelitis suggests MS rather than NMO. A caveat, however, is that a longitudinally extensive lesion may “break up” into noncontiguous segments over months or years. Therefore, as with brain MRI scans, it may be necessary to obtain and evaluate a patient’s older MRI scan performed during an acute myelitis attack. Although most patients with Devic’s Syndrome have a normal cerebral MRI, inflammatory demyelinating lesions have been found in the spinal cord (3, 4), basal ganglia (5), midbrain, cerebral peduncle (6), internal capsule (7), and thalamus (8). This case had an abnormal MRI findings like non-enhancing MS plaque extending from C1-C5 level of spinal cord with possible early cord atrophy.

All patients should have blood tests for the presence of NMO-IgG, the third major diagnostic criterion. A negative test does not exclude NMO (the test is about 70-75% sensitive) but a positive test essentially ‘rules in’ the diagnosis. The test may be obtained through Mayo Medical Laboratories:
(<http://www.mayoreferenceservices.org/mrs/mml/index.asp>)

Although no longer part of the formal diagnostic criteria, lumbar puncture for CSF analysis is useful because the detection of an unusual pleocytosis (>50 WBC) or polymorphonuclear cells suggests a higher likelihood of NMO than of MS. In patients with single or recurrent LETM but without a history of visual loss, visual evoked potentials occasionally detect asymptomatic visual pathway impairment supportive of optic-spinal pattern demyelinating disease. The need for additional diagnostic testing to evaluate for competing disorders in the differential diagnosis of the NMO syndrome (e.g., sarcoidosis, paraneoplastic disease, infections) depends on the individual scenario.

Treatment

Acute optic neuritis or myelitis:

- 1) Corticosteroids: IV methylprednisolone 1000 mg/d (or equivalent) for 5 or more days
- 2) Plasmapheresis for attacks that progress or are refractory to corticosteroid therapy¹⁷⁻¹⁹

The treatment of this case always has a good response to IV methylprednisolone, so she has never underwent plasmapheresis.

Attack prevention:

There are no preventative therapies with efficacy demonstrated by controlled trials in NMO. Most agree that long-term immunosuppression is required for established NMO.²⁰ It has also been recommended for NMO-IgG seropositive patients with single LETM episodes because of the high risk for relapse.¹⁴

Current options include:

- 1) Azathioprine (2.5-3.0 mg/kg/d) plus prednisone (~1mg/kg/d to be tapered after azathioprine is fully effective)²¹
- 2) Mycophenolatemofetil 1000 mg BID plus prednisone as above
- 3) Rituximab (chimeric anti-CD20 monoclonal antibody)²²
- 4) Mitoxantrone²³
- 5) Intravenous immune globulin (IVIG)²⁴
- 6) Cyclophosphamide

The absolute and relative efficacy of these therapies have not been established. The neurologist of our patient chose azathioprine plus prednisolone for that long-term immunosuppression, due to many relapses of disease.

Table 1: Criteria of Wingerchuck et al.³ for the diagnosis of neuromyelitisoptica

- Absolute criteria Optic neuritis

Acute myelitis

No evidence of clinical disease outside the optic nerve or spinal cord

Supportive criteria Major

(1) negative brain MRI at onset

(criteria of Paty et al.²⁵)

(2) spinal cord MRI with signal

abnormality extending over ≥3

vertebral segments

(3) CSF pleiocytosis of > 50 WBC/mm³

or >5 neutrophils/mm³

- Minor

(1) bilateral optic neuritis

(2) severe optic neuritis with fixed

visual acuity of less than 20/200 in

at least one eye

(3) severe, fixed, attack-related weakness

(MRC grade V2) in one or more limbs

Diagnosis requires all absolute criteria and one major supportive criterion or two minor supportive criteria. CSF: cerebrospinal fluid; WBC: white blood cells.

Table 2: NMO Spectrum Disorders

- Neuromyelitisoptica (2006 definition)

- Limited forms of NMO

- o “Idiopathic” single or recurrent events of longitudinally extensive myelitis

- (≥3 vertebral segment spinal cord MRI lesion)

- o Bilateral simultaneous or recurrent optic neuritis

- Asian optic-spinal MS

- Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease

- Optic neuritis or myelitis associated with “specific” NMO brain lesions (hypothalamic, periventricular, brainstem)

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